

This Page Is Inserted by IFW Operations  
and is not a part of the Official Record

## **BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning documents *will not* correct images,  
please do not report the images to the  
Image Problems Mailbox.**

**THIS PAGE BLANK (USPTO)**



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification <sup>6</sup> : C07D 211/26, 211/56, 211/58, 213/75, 207/09, 233/54, 233/84, 295/18, 313/12, 401/06, 401/12, 405/04, C07C 275/28, 275/34, 313/16, 317/14, 321/28, A61K 31 /17, 31 /445</p>	A1	<p>(11) International Publication Number: WO 96/34856</p> <p>(43) International Publication Date: 7 November 1996 (07.11.96)</p>
<p>(21) International Application Number: PCT/EP96/01836</p> <p>(22) International Filing Date: 27 April 1996 (27.04.96)</p> <p>(30) Priority Data: 95401049.2 5 May 1995 (05.05.95) EP</p> <p>(34) Countries for which the regional or international application was filed: FR et al.</p> <p>(71) Applicants (for all designated States except US): GRELAN PHARMACEUTICAL CO. LTD. [JP/JP]; 4F Takedahoncho Boulevard, 1-7, Nihonbashihoncho 2-chome, Chuoku, Tokyo 103 (JP). LABORATOIRES FOURNIER S.C.A. [FR/FR]; 9, rue Petitot, F-21000 Dijon (FR).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (for US only): BINET, Jean [FR/FR]; 13, rue du Faubourg-Saint-Nicolas, F-21121 Fontaine-lès-Dijon (FR). GUFFROY, Christian [FR/FR]; 20, allée des Champs-Fleuris, F-21121 Fontaine-lès-Dijon (FR). KASAI, Hirotaka [JP/JP]; 201 Hikari-House, 1-40, Hikari-cho 2-chome, Kokubunji-city, Tokyo 185 (JP). WAGATSUMA, Nagatoshi [JP/JP]; B-119 Miyamaedaira Palm-House, 15-1,</p>		<p>Tsuchihashi 6-chome, Miyamae-ku, Kawasaki-city, Kanagawa 216 (JP).</p> <p>(74) Agent: CLISCI, Serge; S.A. Fedit-Loriot &amp; Autres, Conseils en Propriété Industrielle, 38, avenue Hoche, F-75008 Paris (FR).</p> <p>(81) Designated States: AU, CA, HU, JP, KR, NO, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p>Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments. With a request for rectification under Rule 91.1(f).</p>
<p>(54) Title: 2-UREIDO-BENZAMIDE DERIVATIVES</p> <div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;"> <p>(1)</p> </div> <div style="text-align: center;"> <math display="block">-(CH_2)_j-N\begin{matrix} R^3 \\   \\ R^4 \end{matrix} \quad (II)</math> </div> </div> <div style="display: flex; justify-content: space-around; align-items: center; margin-top: 20px;"> <div style="text-align: center;"> <math display="block">-(CH_2)_k-N\begin{matrix} R^5 \\   \\ R^6 \end{matrix} \quad (III)</math> </div> <div style="text-align: center;"> <math display="block">-(CH_2)_m-\text{C}_6\text{H}_4-N-A^1 \quad (IV)</math> </div> <div style="text-align: center;"> <math display="block">\begin{matrix} R^7 \\   \\ -C- \end{matrix} \text{C}_6\text{H}_4-N-A^1 \quad (V)</math> </div> </div> <div style="display: flex; justify-content: space-around; align-items: center; margin-top: 20px;"> <div style="text-align: center;"> <math display="block">-(CH_2)_m-A^2 \quad (VI)</math> </div> <div style="text-align: center;"> <math display="block">\text{C}_6\text{H}_4-N- \quad (VII)</math> </div> </div>		
<p>(57) Abstract</p> <p>This invention is concerned with 2-ureido-benzamide compounds of formula (1), in which R<sup>1</sup> is H, halogen, alkyl, alkoxy or dialkylamino and R<sup>2</sup> is H, halogen, hydroxy, nitro, alkyl, alkoxy, cycloalkylmethoxy, alkylthio, alkylsulfinyl, alkylsulfonyl or formula (II), wherein j, R<sup>3</sup> and R<sup>4</sup> are defined as indicated in the disclosure; X is an alkyl, cycloalkyl, cycloalkylmethyl, alkoxyalkyl or formula (III), wherein k, R<sup>5</sup> and R<sup>6</sup> are defined as indicated in the disclosure; and Y is H or alkyl and Z is formula (IV), (V) or (VI), wherein m is an integer of from 0 to 4, and (VII), A<sup>1</sup> and A<sup>2</sup> are defined as indicated in the disclosure, or -NYR can form a ring; and pharmaceutically acceptable acid addition salts thereof. These compounds are useful as ACAT inhibitors.</p>		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Larvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

## 2-UREIDO-BENZAMIDE DERIVATIVES

### BACKGROUND OF THE INVENTION

#### 1. *Field of the invention*

5           The present invention relates to novel 2-ureido-benzamide derivatives having potent acyl coenzyme A:cholesterol acyltransferase (ACAT: EC2.3.1.26) inhibiting activity, to pharmaceutical composition containing these compounds and to use thereof for the treatment and prevention of atherosclerosis.

10           Ischemic circulatory diseases such as myocardial infarction and cerebral infarction resulting from atherosclerosis have been a major cause of human death. The studies on atherosclerosis have been carried out in the various fields for long years.

15           Recently, it has been found that esterification of intracellular cholesterol is effectively catalyzed by the enzyme : ACAT which is found later in various tissues such as liver, intestine, adrenal and macrophages. It is said that ACAT may be present in all tissues [The Enzymes, 16, 523-539 (1983)].

20           In intestine, ACAT plays a key role in the gastrointestinal absorption of cholesterol. In intestinal mucosal cells, dietary and biliary cholesterol derived from the diet and biosynthesis must be esterified by the action of ACAT before it can be incorporated into the chylomicron particles which are then released into the blood stream [Eur. J. Clin. Invest., 9, 55 (1971)]. Thus inhibition of ACAT in intestinal mucosa appears to block intestinal absorption of cholesterol, resulting in the decrease of blood cholesterol level. However, such an intestinal ACAT inhibitor may involve unfavorable increase of the endogenous cholesterol synthesis and possible ineffectiveness of such inhibitor on patients having no  
25           hyper-function in cholesterol absorption.

          Although the role of ACAT in liver, especially in human, is less clearly known, the ACAT may participate in the synthesis and secretion of VLDL and the control of biliary excretion of cholesterol [J. Lipid Res., 26, 647 (1985)]

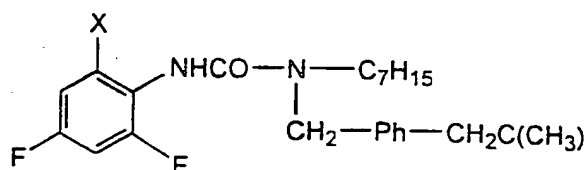
and inhibition of the liver ACAT may result in lowering of the blood lipid level.

Cholesterol esters are a major component of atherosclerotic lesions and also a major storage form of cholesterol in arterial wall cells. Accumulation of cholesterol esters is linked to the foam cell formation which is catalyzed by ACAT in macrophages. Thus, inhibition of the macrophage ACAT may prevent directly the progression of atherosclerotic lesion formation by decreasing the foam cell formation without unfavorable effects as in the case of ACAT inhibition in intestine.

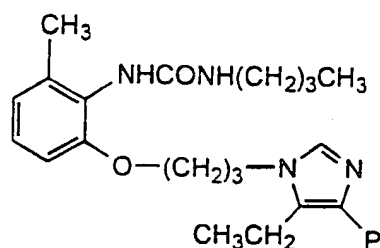
## 2. Description of the prior art

Certain phenylurea derivatives having ACAT inhibiting activity are disclosed as shown below.

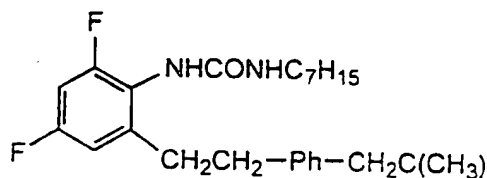
(a) U.S. Patent No.4,623,662 (1986) discloses substituted urea and thiourea compounds such as



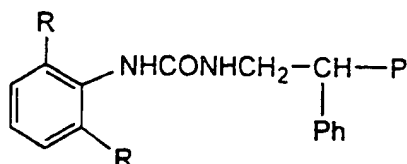
(b) EP Publication No.477,778 (1992) and J. Med. Chem., 36, No. 11, 1641-1653 (1993) disclose benzene, pyridine and pyrimidine derivatives such as



(c) EP Publication No.370,740 (1990) discloses diaryl compounds as inhibitors of ACAT such as



(d) U.S. Patent No.5.116.848 (1992) discloses N-phenylalkyl(thio)urea derivatives such as



(e) A variety of urea compounds can be found in the other literatures, for example, in EP Publication Nos.335,375 (1989), 405,233 (1991) and 447,116 (1991) and in U.S. Patent Nos.4,923,896 (1990), 5,015,644 (1991) and 5,106,873 (1992).

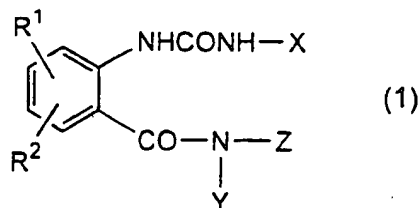
On the other hand, phenylurea derivatives having other pharmacological or agricultural activities such as blood sugar lowering activity, 5-HT M-receptor antagonist activity and herbicidal activity are disclosed in JP Unexamined Publication No. 59-181,257 (1984) [Chem. Abst., 102, No. 78735 (1985)], EP Publication No. 235,878 (1987) and US Patent No. 3,812,168 (1974), respectively. And some organic reactions for phenylurea derivatives are disclosed in literatures such as Indian J. Chem., 266 No. 12, 1133-1139 (1987) and Mh. Chem., 98, No. 3, 633-642 (1967).

However, there are no known literature references disclosing such 2-ureido-benzamide derivatives as those in this invention and their use as ACAT inhibitors for the treatment of atherosclerosis.

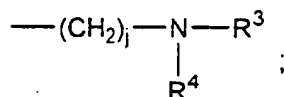
The present inventors synthesized various novel 2-ureido-benzamide compounds having substituents on both of amide and urea(ureido) nitrogen atoms and intensively investigated their activities, and, as the result, found that the compounds have excellent ACAT inhibitory activity and are each expected to be useful as a drug for atherosclerosis and related diseases.

#### SUMMARY OF THE INVENTION

The present invention provides  
(i) a novel 2-ureido-benzamide derivative of the formula (1)

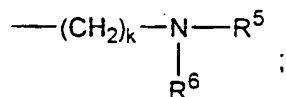


in which  $\text{R}^1$  is H. halogen atom,  $(\text{C}_1\text{-C}_4)$  alkyl,  $(\text{C}_1\text{-C}_4)$  alkoxy or  $(\text{C}_1\text{-C}_4)$  dialkylamino and  $\text{R}^2$  is H. halogen atom. hydroxy, nitro,  $(\text{C}_1\text{-C}_4)$  alkyl,  $(\text{C}_1\text{-C}_4)$  alkoxy,  $(\text{C}_3\text{-C}_6)$  cycloalkylmethoxy,  $(\text{C}_1\text{-C}_4)$  alkylthio,  $(\text{C}_1\text{-C}_4)$  alkylsulfinyl,  $(\text{C}_1\text{-C}_4)$  alkylsulfonyl or



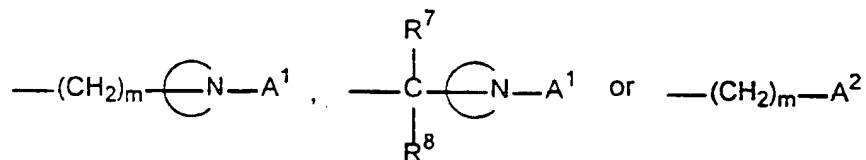
wherein  $j$  is an integer of from 0 to 2 and  $\text{R}^3$  and  $\text{R}^4$  are each independently H,  $(\text{C}_1\text{-C}_4)$  alkyl,  $(\text{C}_1\text{-C}_4)$  alkanoyl,  $(\text{C}_1\text{-C}_4)$  alkylsulfonyl or  $(\text{C}_1\text{-C}_4)$  alkylcarbamoyl, or  $\text{NR}^3\text{R}^4$  can form a pyrrolidine, piperidine, morpholine, imidazole or pyrazole ring;

$\text{X}$  is a  $(\text{C}_3\text{-C}_{15})$  alkyl,  $(\text{C}_3\text{-C}_6)$  cycloalkyl,  $(\text{C}_3\text{-C}_6)$ , cycloalkylmethyl,  $\omega\text{-(C}_1\text{-C}_4)$  alkoxy- $(\text{C}_1\text{-C}_4)$  alkyl group or

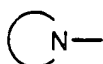


wherein  $k$  is an integer of from 1 to 4 and  $\text{R}^5$  and  $\text{R}^6$  are each independently H,  $(\text{C}_1\text{-C}_6)$  alkyl or  $(\text{C}_1\text{-C}_4)$  alkoxycarbonyl; and

$\text{Y}$  is H or  $(\text{C}_1\text{-C}_4)$  alkyl and  $\text{Z}$  is



wherein  $m$  is an integer of from 0 to 4,

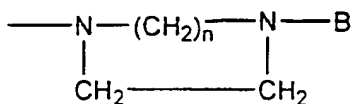


is a pyrrolidinyl or piperidyl ring and  $\text{A}^1$  is a phenyl, benzyl, diphenylmethyl, pyridyl, dibenzoxepinyl, phenoxycarbonyl or



biphenylmethyl group optionally carrying halogen atom, hydroxy, (C<sub>1</sub>-C<sub>7</sub>) alkyl, (C<sub>1</sub>-C<sub>4</sub>) alkoxy, (C<sub>1</sub>-C<sub>4</sub>) alkoxymethyl, phenyl or halogenophenyl, and A<sup>2</sup> is a phenyl, benzyl, diphenylmethyl, dibenzoxepinyl or phenoxy carbonyl group optionally carrying halogen atom, hydroxy, (C<sub>1</sub>-C<sub>7</sub>) alkyl, (C<sub>1</sub>-C<sub>4</sub>) alkoxy, (C<sub>1</sub>-C<sub>4</sub>) alkoxymethyl, phenyl or halogenophenyl, and R<sup>7</sup> is H or (C<sub>1</sub>-C<sub>4</sub>) alkyl and R<sup>8</sup> is (C<sub>1</sub>-C<sub>4</sub>) alkyl or CR<sup>7</sup>R<sup>8</sup> can form a cyclopentyl, cyclohexyl or cycloheptyl ring; or

-NYZ can form a ring



wherein n is an integer of from 1 to 3 and B is a phenyl, diphenylmethyl or dibenzocycloheptenyl group optionally carrying halogen atom or (C<sub>1</sub>-C<sub>4</sub>) alkoxy;

and pharmaceutically acceptable acid addition salts thereof, having excellent ACAT inhibiting activity;

- (ii) an ACAT inhibitor composition which contains anyone of the compounds of the formula (1) and the use of said compounds as ACAT inhibitors ; and
- (iii) a method of producing the compounds of formula (1).

#### DETAILED DESCRIPTION

This invention relates to the compound of formula (1). Referring to the formula (1), the term "halogen" is fluorine (F), chlorine (Cl) or bromine (Br) and the terms "alkyl", "alkoxy" and "alkanoyl" mean straight- and branched-chain alkyl, alkoxy and alkanoyl, respectively. For example, (C<sub>1</sub>-C<sub>4</sub>) alkyl is methyl, ethyl, n- or iso-propyl, n-, iso-, sec- or tert-butyl; (C<sub>1</sub>-C<sub>4</sub>) alkylthio, (C<sub>1</sub>-C<sub>4</sub>) alkylsulfinyl, (C<sub>1</sub>-C<sub>4</sub>) alkylsulfonyl and (C<sub>1</sub>-C<sub>4</sub>) alkylcarbonyl are thio, sulfinyl, sulfonyl and carbonyl substituted by such (C<sub>1</sub>-C<sub>4</sub>) alkyl, respectively; (C<sub>1</sub>-C<sub>4</sub>) alkoxy is methoxy, ethoxy, n- or iso-propoxy or n-, iso-, sec- or tert-butoxy; (C<sub>1</sub>-C<sub>4</sub>) alkoxycarbonyl is carbonyl substituted by such (C<sub>1</sub>-C<sub>4</sub>) alkoxy; and (C<sub>1</sub>-C<sub>4</sub>) alkanoyl is acetyl, propionyl or n- or iso-butyryl. Alkyl higher than C<sub>4</sub>

such as (C<sub>5</sub>-C<sub>15</sub>) alkyl may be represented by pentyl (C<sub>5</sub>), hexyl (C<sub>6</sub>), heptyl (C<sub>7</sub>), octyl (C<sub>8</sub>), nonyl (C<sub>9</sub>), decyl (C<sub>10</sub>), undecyl (C<sub>11</sub>), dodecyl (C<sub>12</sub>), tridecyl (C<sub>13</sub>), tetradecyl (C<sub>14</sub>), pentadecyl (C<sub>15</sub>) and their branched-chain form. Furthermore, referring to the formula (1), the term «(C<sub>3</sub>-C<sub>6</sub>) cycloalkyl» means cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

As mentioned hereinabove, A<sup>1</sup> is a phenyl, benzyl, diphenylmethyl, pyridyl, dibenzoxepinyl, phenoxy carbonyl or biphenylmethyl group which is optionally substituted by one (preferably) or several substituents such as halogen, hydroxy, (C<sub>1</sub>-C<sub>7</sub>) alkyl, (C<sub>1</sub>-C<sub>4</sub>) alkoxy, (C<sub>1</sub>-C<sub>4</sub>) alkoxymethyl, phenyl or halogenophenyl : in a similar manner, A<sup>2</sup> is a phenyl, benzyl, diphenylmethyl, dibenzoxepinyl or phenoxy carbonyl group which is optionally substituted by one (preferably) or several substituents such as halogen, hydroxy, (C<sub>1</sub>-C<sub>7</sub>) alkyl, (C<sub>1</sub>-C<sub>4</sub>) alkoxy, (C<sub>1</sub>-C<sub>4</sub>) alkoxymethyl, phenyl or halogenophenyl.

Preferred embodiments of this invention represented by the formula (1), in view of such as the ACAT inhibiting properties, exhibit one or more of the following features: (a) R<sup>1</sup> is H and R<sup>2</sup> is H, di-substituted amino group or morpholino group; (b) X is (C<sub>3</sub>-C<sub>10</sub>) alkyl, more preferably, (C<sub>3</sub>-C<sub>8</sub>) alkyl; and/or (c) Y is H and Z is a (N-aralkyl) aminoalkyl group such as a (N-diphenylmethyl) piperidyl group with or without intermediary alkylene chain between the nitrogen atom of the amide and the piperidyl ring; or Y and Z considered together with the N atom to which they are bonded are combined to form a ring such as the (N-diphenylmethyl)piperazinyl ring.

Preferred example of the compounds (1) includes:

- 25    2-(N'-n-heptylureido)-5-dimethylamino-N-[(1-diphenylmethylpiperidin-4-yl)-methyl]-benzamide;
- 2-(N'-n-butylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide;
- 2-(N'-n-pentylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide;
- 2-(N'-n-hexylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide;
- 2-(N'-n-heptylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide;

- 2-(N'-n-octylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide;
- 2-(N'-n-butylureido)-N-(1-diphenylmethylpiperidin-4-yl)benzamide;
- 2-(N'-n-hexylureido)-N-(1-diphenylmethylpiperidin-4-yl)benzamide;
- 2-(N'-n-octylureido)-N-(1-diphenylmethylpiperidin-4-yl)benzamide;
- 5 ◦ 2-(N'-n-decylureido)-N-(1-diphenylmethylpiperidin-4-yl)benzamide;
- 2-(N'-n-heptylureido)-N-(1-phenoxy-carbonylpiperidin-4-yl)benzamide;
- 2-(N'-n-heptylureido)-5-hydroxy-N-(3,3-diphenylpropyl)benzamide;
- 2-(N'-n-heptylureido)-N-[2-(1-diphenylmethylpiperidin-4-yl)ethyl]benzamide;
- 2-(N'-n-pentylureido)-N-[2-(1-diphenylmethylpiperidin-4-yl)ethyl]benzamide;
- 10 ◦ 2-(N'-n-hexylureido)-N-[2-(1-diphenylmethylpiperidin-4-yl)ethyl]benzamide;
- 2-(N'-n-heptylureido)-5-dimethylamino-N-(1-diphenylmethylpiperidin-4-yl)-benzamide;
- 1-[2-(N'-n-heptylureido)benzoyl]-4-diphenylmethylhomopiperazine;
- 1-[2-(N'-n-heptylureido)benzoyl]-4-(10,11-dihydro-5H-dibenzo[a,d]cyclohep-
- 15 ten-5-yl)-piperazine;
- 2-(N'-n-heptylureido)-N-(1-diphenylmethylpiperidin-4-yl)benzamide;
- N-(2-bromo-6,11-dihydrodibenz[b,e]oxepin-11-yl)methyl-2-(N'-n-heptylureido)benzamide;
- 2-(N'-n-heptylureido)-5-acetylamino-N-(1-diphenylmethylpiperidin-4-yl)ben-
- 20 zamide;
- N-(3,3-diphenylpropyl)-2-(N'-n-heptylureido)benzamide;
- 1-[2-(N'-n-heptylureido)benzoyl]-4-diphenylmethylpiperazine;
- 2-(N'-n-butylureido)-5-diethylamino-N-[(1-diphenylmethylpiperidin-4-yl)-me-
- thyl]benzamide;
- 25 ◦ 2-(N'-n-butylureido)-5-dimethylamino-N-[(1-diphenylmethylpiperidin-4-yl)-methyl]benzamide;
- 2-(N'-n-butylureido)-5-(pyrrolidin-1-yl)-N-[(1-diphenylmethylpiperidin-4-yl)-methyl]-benzamide;
- 5-dimethylamino-2-(N'-n-propylureido)-N-[(1-diphenylmethylpiperidin-4-yl)-

methyl]-benzamide:

- 2-(N'-butylureido)-5-methoxy-N-[(1-diphenylmethylpiperidin-4-yl)methyl]-benzamide:
- 2-(N'-n-butylureido)-5-ethoxy-N-[(1-diphenylmethylpiperidin-4-yl)methyl]-benzamide:
- 5    ◦ 2-(N'-n-butylureido)-5-cyclopropylmethoxy-N-[(1-diphenylmethylpiperidin-4-yl)methyl]-benzamide;
- 2-(N'-n-butylureido)-5-(morpholin-4-yl)-N-[(1-diphenylmethylpiperidin-4-yl)-methyl]-benzamide:
- 10   ◦ 5-(morpholin-4-yl)-2-(N'-n-propylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]-benzamide;
- 2-(N'-n-butylureido)-5-methylthio-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide:
- 5-n-butylcarbamyloxy-2-(N'-n-butylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]-benzamide:
- 15   ◦ 2-(N'-n-heptylureido)-5-methoxy-N-[(1-diphenylmethylpiperidin-4-yl)methyl]-benzamide;
- 2-(N'-n-heptylureido)-5-(morpholin-4-yl)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]-benzamide:
- 20   ◦ 2-(N'-n-heptylureido)-5-(pyrazol-1-yl)-N-[(1-diphenylmethylpiperidin-4-yl)-methyl]benzamide;
- 2-(N'-n-heptylureido)-5-(pyrrolidin-1-yl)-N-[(1-diphenylmethylpiperidin-4-yl)-methyl]-benzamide;
- 5-ethoxy-2-(N'-n-heptylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]-benzamide:
- 25   ◦ 2-(N'-n-heptylureido)-5-dimethylamino-N-[(1-diphenylmethylpiperidin-3-yl)-methyl]-benzamide;
- 5-(N'-acetyl-N-methyl)amino-2-(N'-n-heptylureido)-N-[(1-diphenylmethylpiperidin-4-yl)-methyl]benzamide;

- 2-(N'-n-heptylureido)-5-dimethylamino-N-[[1-bis(4-fluorophenyl)methylpiperidin-4-yl]-methyl]benzamide;
- 2-(N'-n-heptylureido)-5-dimethylamino-N-[[1-bis(4-methoxyphenyl)methylpiperidin-4-yl]-methyl]benzamide;
- 5 ◦ 2-(N'-n-heptylureido)-5-dimethylamino-N-[1-(2-biphenylmethylpiperidin-4-yl)methyl]-benzamide;
- 5-dimethylamino-2-(N'-n-pentylureido)-N-[(1-diphenylmethylpiperidin-4-yl)-methyl]benzamide;
- 2-(N'-3-methoxypropylureido)-5-dimethylamino-N-[(1-diphenylmethylpiperidin-4-yl)-methyl]benzamide;
- 10 ◦ 2-(N'-3-methoxypropylureido)-5-(morpholin-4-yl)-N-[(1-diphenylmethylpiperidin-4-yl)-methyl]benzamide;
- 2-(N'-cyclopropylmethylureido)-5-(morpholin-4-yl)-N-[(1-diphenylmethylpiperidin-4-yl)-methyl]benzamide;
- 15 ◦ 2-(N'-n-butylureido)-5-methylsulfinyl-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide;
- 2-(N'-n-butylureido)-5-methylsulfonyl-N-[(1-diphenylmethylpiperidin-4-yl)-methyl]benzamide.

The above compounds (1) may be in the form of their pharmaceutical  
20 acceptable acid addition salts which are included within the scope of this invention. Preferred example of the salts include non-toxic salts with inorganic and organic acids, such as hydrochloric, hydrobromic, sulfuric, phosphoric, acetic, lactic, tartaric, citric, fumaric, malic, maleic, succinic, methanesulfonic, benzenesulfonic and p-toluenesulfonic acids. Preparation of the salts can be  
25 carried out in accordance with well known techniques for forming salts.

This invention also relates to a method of or use for reducing the cholesterol content of the arterial walls and treating atherosclerosis and related diseases of mammals which comprises administering to said mammals an effective amount of a compound as recited above. The compounds (1) have potent

ACAT inhibiting activity with weak toxicity as shown in the following test example. ACAT catalyzes the esterification of cholesterol with higher fatty acids and it plays an important role in the absorption of cholesterol and in the intracellular accumulation of cholesterol esters. ACAT inhibitor can reduce  
5 absorption of dietary cholesterol and intracellular cholesterol ester accumulation in the arterial wall, thereby, lowering the blood cholesterol level with retarding the build-up of atherosclerotic lesions. Accordingly, the compounds (1) of this invention are useful as safe prophylactic and therapeutic agents for hypercholesterolemia, atherosclerosis and diseases resulting from these (e.g.  
10 ischemic heart diseases such as myocardial infarction, cerebrovascular diseases such as cerebral infarction and cerebral apoplexy) in mammals (e.g. mouse, rat, rabbit, dog, monkey, human).

This invention further relates to pharmaceutical compositions which comprise an effective anti-atherosclerotic amount of a compound as recited above.  
15 For prophylactic or therapeutic use vis-a-vis the above diseases, the compounds of formula (1) are preferably presented with pharmaceutically acceptable appropriate carriers, excipients or diluents as pharmaceutical formulations such as powders, granules, tablets, capsules or injectable solutions, which can be prepared by any of the well known techniques of pharmacy and administered either orally or non-  
20 orally.

For the purpose of inhibiting cholesterol absorption or accumulation, the oral route of administration may be preferred. The amount of a compound of formula (1) which is required to achieve the desired biological effect will, of course, depend on the kind of compound (1), the mode of administration, the  
25 clinical condition and age of the recipient and the other factors. In general, a daily dose per kilogram of body weight is expected to lie in the range of from 10 $\mu$ g to 100mg, typically from 50 $\mu$ g to 50mg, and such daily dose is preferably administered as a single dose or in two or three divided doses.

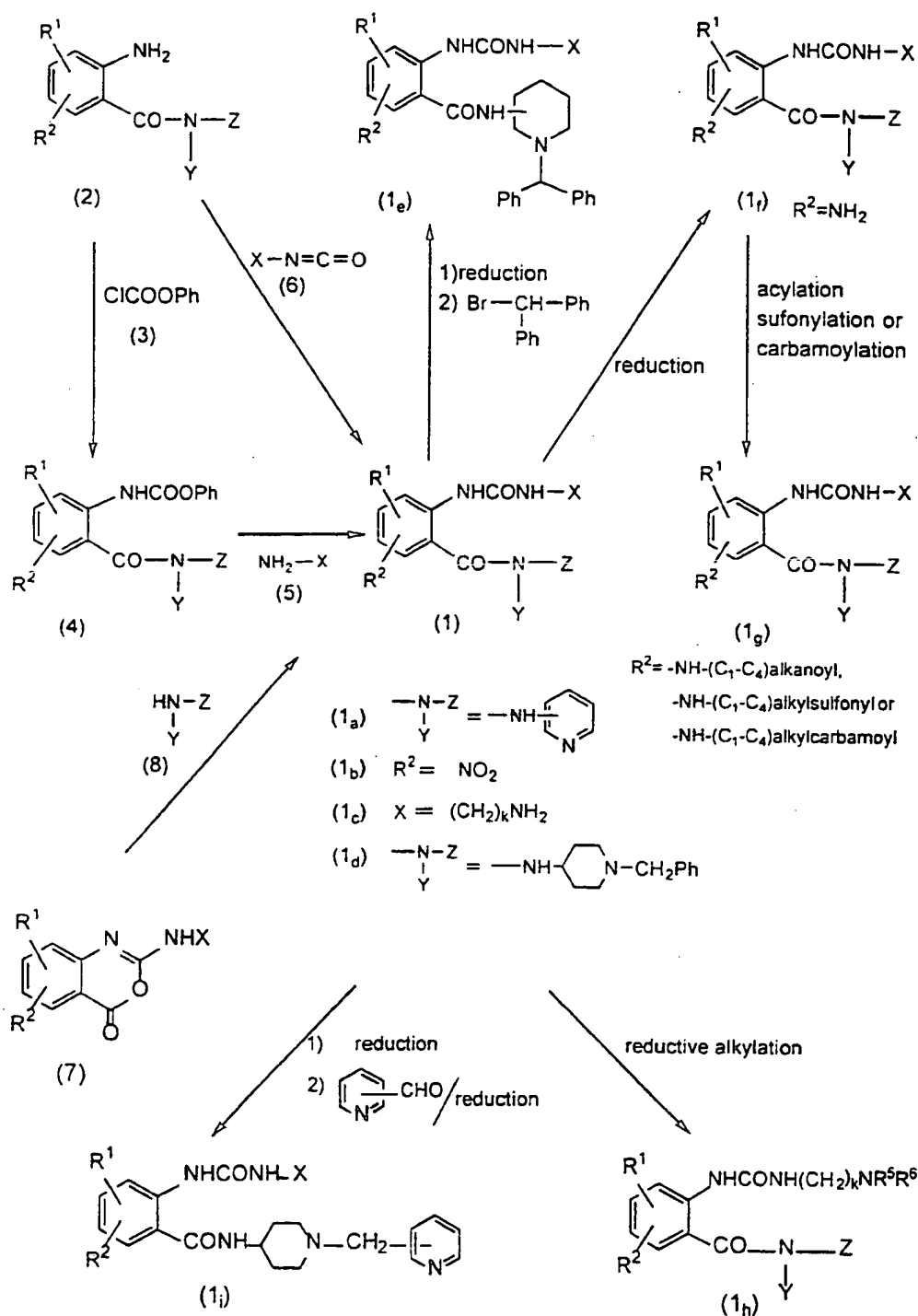
This invention still further relates to process for preparing compounds

as recited above.

Preparation Process for the Compound (I)

There are several alternate approaches to the preparation of the compounds in this invention.

- 5           A. Synthesis of the 2-ureido-benzamides. 2-Ureido-benzamide derivatives of the formula (I) can be prepared by, for instance, the following processes which are outlined in Reaction Scheme I.

**Reaction Scheme I**

(The Symbols in the above formula are as defined hereinabove and



phenyl and pyridyl ring may be optionally substituted as defined hereinabove)

A1) The reaction of the 2-amino-benzamide (2) with formic acid ester halide such as phenyl chloroformate (3) is generally carried out in a solvent in the presence of a base. A suitable base may be for instance an organic base such as pyridine, triethylamine, picoline, 4-dimethylaminopyridine and N,N-diethylaniline and an inorganic base such as potassium carbonate. Among the suitable solvent are used any inert solvent to the reaction, for instance, benzene, toluene, chloroform and dichloromethane. The reaction is generally conducted at an appropriate temperature of -20°C to the boiling point of the solvent which is used.

10 The 2-phenoxy-carbonylamino-benzamide (4) thus obtained is reacted with the amine (5) to give 2-ureido-benzamide (1). The reaction is generally carried out in an appropriate solvent such as benzene, toluene, chloroform and dichloromethane. The amine (5) may be prepared by a known method, for example, by the processes described by C. A. Buecheler et. al. in Survey of Organic Synthesis,

15 394-459 (1977) or modifications thereof.

A2) Alternatively, the 2-ureido-benzamide (1) can be prepared by reacting 2-amino-benzamide (2) with the isocyanate (6). This reaction is conducted in the absence of a solvent or in an inert solvent such as ethyl acetate, dichloromethane, chloroform, tetrahydrofuran, acetonitrile, benzene, toluene and N,N-dimethylformamide. The reaction temperature is generally comprised between room temperature and the refluxing temperature of the solvent which is used. In the absence of a solvent, this reaction can be carried out by heating the 2-amino-benzamide(2) with the isocyanate (6) directly at 90-250°C. The isocyanate (6) is obtained by reacting the corresponding carboxylic acid with an azide compound such as diphenylphosphoryl azide in the presence of a tertiary amine such as triethylamine, pyridine and picoline in an appropriate solvent such as acetonitrile and chloroform.

25

A3) Further, the compound (1) can be prepared by reacting the benzoxazin (7) with the amine (8) in an appropriate solvent such as benzene,

toluene, N,N-dimethylformamide, acetonitrile and chloroform. The temperature is generally comprised between room temperature and the boiling point of the solvent which is used. The benzoxazin (7) may be obtained by a known method [e. g. J. Heterocyclic Chemistry, 19, 267 (1982) and EP Patent No. 147,211 (1985)] or its modified method. The amine (8) is commercially available or readily prepared by a known method described for instance in US Patent No. 4,267,318 or a modification thereof.

B. Conversion of the 2-ureido-benzamides. Certain compounds of 2-ureido-benzamide derivatives of the formula (1) prepared by the above mentioned processes A1), 2) and 3) are then further converted to the another 2-ureido-benzamide derivatives. For example, the compounds described as structures (1<sub>a</sub>), (1<sub>b</sub>), (1<sub>c</sub>) and (1<sub>d</sub>) are successfully converted to the objective 2-ureido-benzamide derivatives of the formulae (1<sub>e</sub>), (1<sub>f</sub>), (1<sub>g</sub>), (1<sub>h</sub>) and (1<sub>i</sub>) by the following processes which are also outlined in Reaction Scheme I.

B1) The N-pyridyl-2-ureido-benzamide (1<sub>a</sub>) can be reduced to the corresponding N-piperidyl compound and then reacted with diphenylmethyl halide such as bromodiphenylmethane in the presence of a base such as potassium carbonate in a solvent such as dimethyl sulfoxide to give the N-(N-diphenylmethyl)piperidyl-2-ureido-benzamide (1<sub>e</sub>). The reduction can be effectively performed by catalytic reduction using an appropriate catalyst such as platinum and platinum oxide under hydrogen atmosphere at an appropriate pressure of 20-100 psi in a solvent such as acetic acid.

B2) The 5-amino-2-ureido-benzamide (1<sub>f</sub>) may be prepared by reducing 5-nitro-2-ureido-benzamide (1<sub>b</sub>). This reaction can be conducted in the manner of catalytic reduction using appropriate catalyst or can be conducted in the presence of a reducing agent. As such catalyst, there may be mentioned, for example, palladium on charcoal, platinum on charcoal and Raney nickel. As examples of said reducing agent is metal (e. g. zinc, iron and tin) in an acid such as hydrochloric acid, acetic acid and aqueous sulfuric acid. The reduction is

generally carried out under hydrogen atmosphere at an appropriate pressure of ambient to  $5\text{kg/cm}^2$  in a solvent such as methanol, ethanol, acetic acid and ethyl acetate at an appropriate temperature of room temperature to  $100^\circ\text{C}$ . The reaction using the reducing agent is generally carried out in the similar manner to a known method described for instance in J. Org. Chem., 31, 684(1966).

B3) Alternatively, 5-amino-2-ureido-benzamide ( $1_f$ ) thus obtained may be converted to the 5-N-acylated, 5-N-sulfonylated or 5-N-carbamoylated compound of the formula ( $1_g$ ). The compound ( $1_f$ ) can be acylated with an acid anhydride such as acetic anhydride or an acid chloride such as acetyl chloride in the presence of an appropriate base in a solvent such as dichloromethane and chloroform. Useful as said base are cited organic bases, for instance, triethylamine, pyridine and N,N-diethylaniline. The reaction temperature is generally comprised between  $0^\circ\text{C}$  and the boiling point of the solvent which is used.

Sulfonylating the compound ( $1_f$ ) can be performed in the similar manner as the above mentioned acylating, but replacing acid anhydride or acid chloride with alkylsulfonyl chloride such as methanesulfonyl chloride.

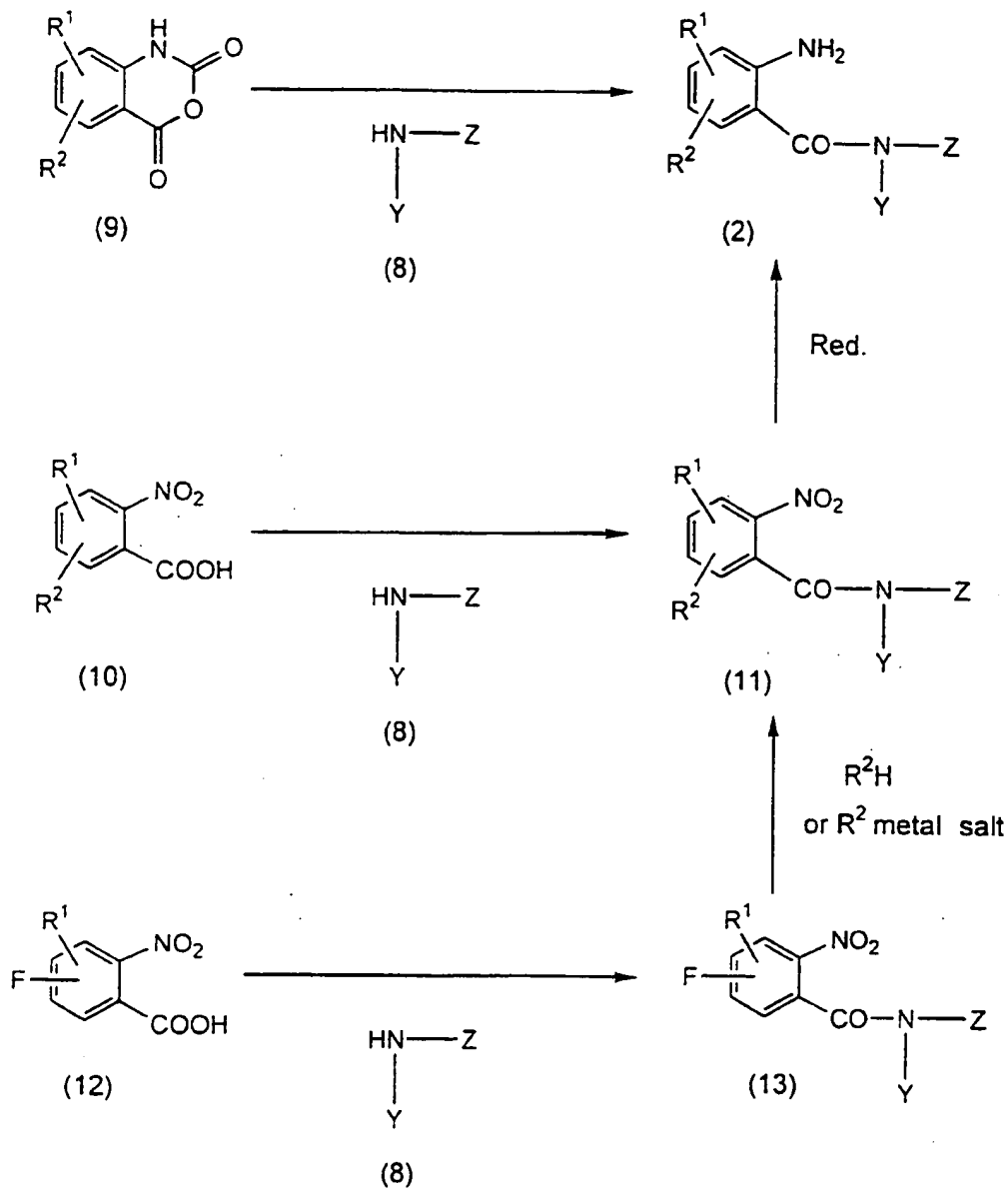
The compound ( $1_f$ ) can be converted to the 2,5-diureido-benzamide according to the similar manner as for the preparation process A2) by reacting with the corresponding isocyanate.

B4) 2-(N'-Alkylaminoalkylureido)-benzamide ( $1_h$ ) may be prepared by reductive alkylation of the 2-(N'-aminoalkylureido)benzamide ( $1_e$ ) with the corresponding carbonyl compound. The reaction can be carried out by the use of a reducing agent such as sodium cyanoborohydride, sodium borohydride or lithium cyanoborohydride in an appropriate solvent such as methanol, ethanol and ethyl ether at an appropriate temperature of from  $-20^\circ\text{C}$  to the boiling point of the solvent which is used.

B5) The benzyl group of the N-benzylpiperidyl-2-ureido-benzamide ( $1_d$ ) is removed by reduction and the resulting N-piperidyl-2-ureido-benzamide

may be reacted with the corresponding formyl pyridine in the presence of a reducing agent such as sodium cyanoborohydride to give the N-pyridylmethylpiperidyl-2-ureido-benzamide (1<sub>i</sub>). The reduction of the compound (1<sub>d</sub>) is generally performed by hydrogen over an appropriate catalyst such as  
5 palladium on charcoal.

C. Preparation of the intermediates : The 2-amino-benzamide (2) which is important as a starting compound for the preparation of the 2-ureido-benzamide (1) can be synthesized, for example, by the following processes outlined in Reaction Scheme II.

Reaction Scheme II

C1) 2-Amino-benzamide (2) can be prepared by reacting the isatoic anhydride (9) with the amine (8) in a solvent such as dichloromethane and chloroform at an appropriate temperature of from room temperature to the boiling point of the solvent which is used.

C2) The condensation reaction of the 2-nitrobenzoic acid (10) with the

amine (8) can be carried out in the presence of a condensing agent in an inert solvent such as dichloromethane, chloroform and tetrahydrofuran at an appropriate temperature of from 0°C to room temperature. The useful condensing agents are 1,3-dicyclohexyl-carbodiimide, N-ethyl-N'-(3-dimethylaminopropyl) carbodiimide and 1,1-carbonyl-diimidazole. The 2-nitrobenzamide (11) thus  
5 obtained is reacted with a reducing agent to give the 2-amino-benzamide (2). This reductive reaction can be conducted essentially in the same manner as the preparation process B2) mentioned above.

C3) The condensation of the 2-nitrobenzoic acid (12) with the amine  
10 (8) can be carried out in the presence of a condensing agent in the same manner as the preparation process C2) or by using thionyl chloride, compound (12) to convert into the acid chloride, followed by reacting with the amine (8). The fluorine substituent on 5-position of the 2-nitrobenzamide (13) thus obtained is substituted for other substituents by reacting with  $R^2H$  (e.g. monomethylamine,  
15 dimethylamine, diethylamine, di-n-propylamine, di-n-butylamine, pyrrolidine, piperidine, morpholine, pyrazole, imidazole) or  $R^2$  metal salt (e.g. sodium methoxide, sodium ethoxide, sodium thiomethoxide, sodium thioethoxide) in an inert solvent such as tetrahydrofuran, dioxane and N,N-dimethylformamide with or without a sealed tube at an appropriate temperature (from ambient to refluxed  
20 temperature). The 2-nitrobenzamide (11) thus obtained is reacted with reducing agents in the same manner as the preparation process B2) to give the amino-benzamide (2).

The desired compounds (1) thus obtained can be purified and recovered by using per se known separation or purification procedures (e. g.  
25 concentration, solvent extraction, column chromatography, recrystallization).

#### Activity

The following pharmacological test results indicate that the 2-ureido-benzamide derivatives (1) according to the inventions are of great utility.

1. Acyl-CoA:cholesterol acyltransferase (ACAT) inhibiting activity.

## [Test method]

(1) *In-vitro* test using Hep G2 microsome.

ACAT enzyme fraction was prepared from microsome of human derived hepatoma Hep G2 cell according to Sandra's method [Journal of Lipid Research, 27, 875 (1986)].

Microsome was suspended at a concentration of 200 $\mu$ g protein/ 20 $\mu$ l in 0.1M phosphate buffer solution (pH7.4) and the suspension was preincubated at 37°C for 5 minutes after addition of 10 $\mu$ l of each test compound dissolved in 0.1M phosphate buffer solution containing bovine serum albumin (BSA). Then, the reaction was initiated by the addition of 5nmoles of labeled [ $^{14}$ C]-oleoyl-CoA dissolved in 20 $\mu$ l of the said phosphate buffer solution containing BSA and the reaction was stopped by the addition of 20 $\mu$ l of 2N HCl after 10 minutes. [ $^{14}$ C] cholesterol-oleate formed was separated by thin-layer chromatography and the radioactivity was counted with liquid scintillation counter.

ACAT inhibitory activities of the test compounds were shown as IC<sub>50</sub> values.

(2) *In-vitro* test using THP-1 intact cell.

About 2 million cells of human leukemia cell line, THP-1 were seeded in a well with 2ml of medium and differentiated into macrophage-like cells by phorbol ester. Then, the cells were washed with phosphate-buffered saline (PBS) solution and the medium was replaced by fresh medium supplemented with 10% of lipoprotein-deficient serum. After the addition of each test compound dissolved in dimethyl sulfoxide and 100 $\mu$ g protein-containing human low density lipoprotein (LDL), the reaction was initiated by the addition of 10nmoles of labeled [ $^{14}$ C]oleic acid and 10nmoles of oleic acid complexed with BSA in PBS solution. After 22 hours, the reaction was stopped by removal the medium and CHCl<sub>3</sub>-MeOH (2:1) were added to the cell suspension in order to extract lipids.

Intracellular [ $^{14}\text{C}$ ] cholesterol-oleate formed was separated by thin-layer chromatography and the radioactivity was counted with lipid scintillation counter.

ACAT inhibitory activities of the test compounds were shown as  $\text{IC}_{50}$  values.

(3) *In-vivo* test using mouse peritoneal macrophages.

Male mice were fed a standard powder diet containing the test compounds for 16 days. After 14 and 15 days on this diet, aggregated-LDL (containing 4mg cholesterol) prepared from LDL receptor deficient KHC rabbit and [ $^{14}\text{C}$ ] oleic acid together with the said aggregated-LDL (containing 0.5mg cholesterol) were injected into the peritoneal cavity of these animals, respectively. After 16 days on this treatment, peritoneal macrophages were harvested by peritoneal lavage with PBS solution and  $\text{CHCl}_3$ -MeOH (2:1) were added to the cell suspension in order to extract lipids. Formed [ $^{14}\text{C}$ ] cholesterol oleate was separated by thin-layer chromatography and the radioactivity was counted.

ACAT inhibitory activities of the test compounds were shown as inhibiting percentage referred to control group.

(4) *In vitro* test using THP-1 microsome.

ACAT enzyme fraction was prepared from microsome of human leukemia THP-1 cell as described above in method (1).

Microsome was suspended at a concentration of 200 $\mu\text{g}$  protein / 20 $\mu\text{l}$  in 0.1M phosphate buffer solution (pH7.4) and the suspension was preincubated at 37 5 minutes after addition of 10 $\mu\text{l}$  of each test compound dissolved in 0.1M phosphate buffer solution containing BSA. Then, the reaction was initiated by the addition of 5nmoles of labeled [ $^{14}\text{C}$ ] oleoyl-CoA dissolved in 20  $\mu\text{l}$  of said phosphate buffer solution containing BSA and the reaction was stopped by the addition of 20  $\mu\text{l}$  of 2N HCl after 10 minutes. [ $^{14}\text{C}$ ] cholesterol-oleate formed was separated by thin-layer



chromatography and the radioactivity was counted with liquid scintillation counter.

ACAT inhibitory activities of the test compounds were shown as  $IC_{50}$  values.

- 5 (5). Bioavailability assessment of ACAT inhibitors by their «*ex vivo*» activity.

Five non-fasted female mice weighing 19.0 - 20.0 g were administered at 10 a.m. *per os* 30 mg/kg of oral suspension (1% carboxymethyl cellulose sodium salt (CMC-Na) 0.2% Tween 80). Blood samples were collected 0.5, 1, 1.5, 2, 6 hour postdose. Serum were harvested after gentle centrifugation and stored at -20.

The following day, 10  $\mu$ l serum were preincubated at 37 for 5 minutes with 20  $\mu$ l of THP-1 microsomal ACAT and then incubated 10 minutes with 20  $\mu$ l of radiolabeled oleoyl-CoA as described above in method (4). The serum is used instead of the drug solution.

- 15 ACAT inhibitory activities of the test compounds were shown as maximum inhibition percentages ( $I_{max}$ ).

- (6) *In vivo* test using peritoneal macrophages in C57BL/6J mice.

A standard pellet diet fed female C57BL/6J mice were administered at 10 a.m. *per os* 30 mg/kg/day of oral suspension (1% CMC-Na 0.2% Tween 80) for 4 days. Thioglycollate and [ $^{14}$ C] cholesterol were injected into the peritoneal cavity at the 2nd and 4th day, respectively. Four hours after the injection of labeled cholesterol, mice were sacrificed for the collection of peritoneal macrophages. Lipid was extracted, formed [ $^{14}$ C] cholesterol-ester was separated by thin-layer chromatography and radioactivity was counted as described above in method (3).

*In vivo* ACAT inhibitory activities on macrophages were expressed as percentage of inhibition compared to control group.

#### [Results]

- (1) and (2): As can be seen in Table 1, the compounds caused a significant

inhibitory activity on ACAT.

(3): As can be seen in Table 2, the compounds caused a significant inhibitory activity on ACAT.

(4) and (5): As can be seen in Table 3, the compounds showed a significant  
5 inhibitory activity on ACAT and high bioavailability.

(6) As can be seen in Table 4, the compounds caused a significant inhibitory activity on ACAT.

Table 1

IC<sub>50</sub> values of ACAT inhibitors on ACAT of HepG2 microsome and THP-1 cells.

	IC <sub>50</sub> (μM)	
	Hep G2 (microsome)	THP1 (intact cell)
1	0.6	0.07
2	1.0	0.1
3	0.9	0.1
4	0.9	0.09
5	1.6	0.07
6	1.6	0.05
12	8.0	0.7
19	3.6	0.1
28	1.2	0.1
29	1.6	0.2
30	1.2	0.2
31	0.8	0.2
45	2.8	0.8

**Table 2**

Inhibition rate on ACAT of macrophage

Test Compound (Example No.)	Inhibition rate(%) (macrophages)
1	65
5	64
E5324 <sup>*a</sup>	38
CI976 <sup>*b</sup>	50
Notes :	
<sup>*a</sup> : N-[6-methyl-2-{3-(5-ethyl-4-phenyl-1H-imidazol-1-yl)propoxy}]-phenyl-N'-butylurea	
<sup>*b</sup> : 2,2-dimethyl-N-(2,4,6-trimethoxyphenyl)-dodecanamide	

**Table 3**

Test compound (Example No.)	IC <sub>50</sub> (μM) THPI microsome	I <sub>max</sub> (%) Ex vivo
62	0.03	62.57
63	0.05	68.52
64	0.2	43.14
65	0.06	37.43
66	0.08	77.59
67	0.05	51.97
68	0.03	50.51
69	0.03	40.11
70	0.06	---
71	0.09	81.1

Table 3 (continuation)

73	0.02	38.17
77 (b)	0.05	41.37
79	0.22	63.26*
80	0.17	---
81	0.04	74.11*
82	0.1	50.15
83	0.27	---
84	0.1	5.75
85	0.06	11.33
86	0.04	---
87	0.2	---
89	0.06	---
91	0.08	61.47
92	0.3	---
93	0.04	24.17
94	0.1	28.35
96	0.08	20.45
100	0.04	39.01
103	0.09	---
104	0.1	---
105	0.1	---
106	0.22	---
109	0.4	---
111(a)	0.1	62.01
(b)	0.09	63.56
112	0.2	---
* : Compounds were tested at 100mg/kg in a suspension of 0.5% CMC-Na.		

Table 4

Test Compound (Example No.)	Inhibition rate(%) (macrophages)
[Experiment 1]* <sup>a</sup>	
1	81.0
63	72.3
66	73.5
E5324* <sup>b</sup>	55.4
PD132301-2* <sup>c</sup>	93.2
[Experiment 2]* <sup>a</sup>	
63	61.0
70	73.0
71	73.5
Notes :	
*a : Two separate experiment were carried out on same method.	
*b : N-[6-methyl-2-[3-(5-ethyl-4-phenyl-1H-imidazol-1-yl)propyloxy]]-phenyl-N'-butylurea	
*c : N-[2,6-bis(1-metnylethyl)-phenyl]-N'-[[1-[4-(dimethylamino)-phenyl] cyclopentyl]methyl]urea, hydrochloride	

## 2. Test for toxicity.

## 5 [Test method]

- (1) Acute toxicity : Nine compounds (Example No. 1, 2, 5, 6, 12, 19, 28, 31 and 45) were tested by using male ICR strain mouse weighing  $23.0 \pm 0.7$ g. Each test compound was suspended with 0.5% CMC-Na and orally administered in a dose of 1000mg/10ml/kg of body weight, and general signs were

observed for seven days. Seven days after administration of each test compounds, no macroscopic changes were observed on any organs at autopsy.

- (2) Acute toxicity : Five compounds (Example No.1, 63, 66, 70, 71) were tested by using female C57BL/6J mice. Each test compound was suspended in 1% CMC-Na containing 0.2% Tween 80 solution and orally administered at a dose of 2000mg/20ml/kg of body weight.

[Results]

- (1) No toxicological findings were observed in each test compound treated group.

- (2) The lethal dose was not reach at 2000mg/kg.

The following Preparations and Examples are further illustrative of the present invention. It is to be noted, however, that such Examples are by no means limitative of the scope of the invention. All compounds were identified by proton NMR spectrometry, mass spectrometry and/or other analytical or physical technique.

Preparations

Preparation 1 to 11 and Preparation 21 to 23 are described for synthesis of the amine (8) and Preparation 12 to 20 and Preparation 24 to 33 are described for synthesis of the 2-amino-benzamide (2), both of which are intermediates for the preparation of the objective 2-ureido-benzamide (1).

**PREPARATION 1**

**4-Aminomethyl-1-diphenylmethylpiperidine**

Step 1) : Bromodiphenylmethane (2.5g, 0.01mol) in DMF (10ml) was added dropwise at 0-5°C to a mixture of isonipecotamide (1.3g, 0.01mol) and  $K_2CO_3$  (1.4g) in DMF (25ml). The reaction mixture was stirred for 2 hours at 0-5°C, then poured into water. The mixture was extracted with ethylether, then the extract was washed with brine, dried ( $MgSO_4$ ) and evaporated to give 1-diphenylmethylpiperidine-4-carboxamide (66%) : mp 150°C.

Step 2) : 1-Diphenylmethylpiperidine-4-carboxamide (1.5g, 5.1mmol) was added dropwise to a suspension of  $\text{LiAlH}_4$  (0.4g, 10.5mmol) in THF (30ml). The mixture was heated at 70°C for 3 hours and then cooled. To the mixture, water (0.4ml), 15 % NaOH solution (0.4ml) and water (1.2ml) were added dropwise in order, and insoluble materials were filtered off. The filtrate was concentrated. The residue was purified by column chromatography on silica gel (10% methanol in dichloromethane) to give 4-aminomethyl-1-diphenylmethylpiperidine (57.0%) as colorless crystals : mp 80°C.

## PREPARATION 2

### 4-(2-Aminoethyl)-1-diphenylmethylpiperidine

Step 1) : In a similar manner to that of Preparation 1. but replacing isonipecotamide and 1-diphenylmethylpiperidine-4-carboxamide with ethyl isonipecotate and ethyl 1-diphenylmethyl-4-piperidinecarboxylate respectively, 1-diphenylmethyl-4-hydroxymethylpiperidine was prepared.

Step 2) :  $\text{SOCl}_2$  (0.6ml, 8.2mmol) was added dropwise to a solution of 1-diphenylmethyl-4-hydroxymethylpiperidine (1.0g, 3.6mmol) in benzene (7ml) at room temperature. The mixture was refluxed for 18 hours and then concentrated. The residue was dissolved in ethyl acetate, washed with 5 % NaOH solution, dried ( $\text{MgSO}_4$ ) and concentrated. The residue was recrystallized (ethyl acetate /ether /hexane) to give 1-diphenylmethyl-4-chloromethylpiperidine (70.1%) : mp 73-75°C.

Step 3) : NaCN (2.5g, 51mmol) was added to a solution of 1-diphenylmethyl-4-chloromethyl-piperidine (8.9g, 29.7mmol) in dimethyl sulfoxide (DMSO) (100ml). The mixture was heated at 60°C for 20 hours and then poured into 3%  $\text{NaHCO}_3$  solution and extracted with ethyl acetate. The organic layer was dried ( $\text{MgSO}_4$ ) and concentrated. The residue was purified by column chromatography on silica gel (10% ethyl acetate in hexane) to give 4-cyanomethyl-1-diphenylmethylpiperidine (61.4%) : mp 103-104°C and 3-(2-cyanoethyl)-1-diphenylmethyl pyrrolidine (20.9%) : oil.

Step 4) : In a similar manner to that of Preparation 1 Step 2), but replacing 1-diphenyl-methylpiperidine-4-carboxamide with 4-cyanomethyl-1-diphenylmethylpiperidine. 4-(2-aminoethyl)-1-diphenylmethylpiperidine was obtained as an oily product.

5 **PREPARATION 3**

**4-(3-Aminopropyl)-1-diphenylmethylpiperidine**

Step 1) : In a similar manner to that of Preparation 1 Step 1), but replacing isonipecotamide with 4-(2-hydroxyethyl)piperidine. 1-diphenylmethyl-4-(2-hydroxyethyl)piperidine was prepared.

10 Step 2) : In a similar manner to that of Preparation 2 Step 2) to 4), but replacing 1-diphenylmethyl-4-hydroxymethylpiperidine with 1-diphenylmethyl-4-(2-hydroxyethyl)piperidine. 4-(3-aminopropyl)-1-diphenylmethylpiperidine was prepared.

**PREPARATION 4**

15 **3-(3-Aminopropyl)-1-diphenylmethylpyrrolidine**

In a similar manner to that of Preparation 1 Step 2), but replacing 1-diphenylmethyl-piperidine-4-carboxamide with 3-(2-cyanoethyl)-1-diphenylmethylpyrrolidine which was obtained according to Preparation 2 Step 3), 3-(3-aminopropyl)-1-diphenylmethyl-pyrrolidine was prepared.

20 **PREPARATION 5**

**1-Diphenylmethyl-homopiperazine**

In a similar manner to that of Preparation 1 Step 1). 1-diphenylmethylhomopiperazine was prepared from homopiperazine and bromodiphenylmethane.

25 **PREPARATION 6**

**4-(10,11-Dihydrodibenzo[a,d]hepten-5-yl)piperazine**

In a similar manner to that of Preparation 1 Step 1). 4-(10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5-yl)piperazine was prepared from piperazine and 5-chlorodibenzosuberane.



**PREPARATION 7****11-Aminomethyl-2-bromo-6,11-dihydrodibenz[b,e]oxepin**

A solution of  $\text{AlCl}_3$  (1.0g, 7.5mmol) in dry ether (10ml) was added rapidly to a solution of  $\text{LiAlH}_4$  (0.5g, 13.2mmol) in dry ether (13ml). After 5 minutes, a suspension of 2-bromo-11-cyano-6,11-dihydrodibenz[b,e]oxepin (2.0g, 6.7mmol) in dry ether (100 ml) was added to the mixture of hydride. The reaction mixture was stirred for 4.5 hours. Water and Rochelle Salt were added to the reaction mixture. The mixture was poured into ether. The organic layer was dried ( $\text{MgSO}_4$ ) and concentrated. The residue was purified by column chromatography on silica gel to give 11-aminomethyl-2-bromo-6,11-dihydrodibenz[b,e]oxepin (48.9%).

**PREPARATION 8****11-(4-Aminopiperidin-1-yl)-2-bromo-6,11-dihydrodibenz[b,e]oxepin**

Step 1) : A solution of 2,11-dibromo-6,11-dihydrodibenz[b,e]oxepin (8.0g, 22.7mmol) in benzene (100ml) was added by portions to the solution of 1,4-dioxo-8-azaspiro[4,5]decane (6.5g, 45.4mmol) in acetonitrile (50ml) in an ice bath. The reaction mixture was stirred at room temperature for 1 hour and then poured into water. The organic layer was washed with water, then dried ( $\text{MgSO}_4$ ) and concentrated to give 11-(1,4-dioxo-8-azaspiro[4,5]decane-1-yl)-2-bromo-6,11-dihydrodibenz[b,e]oxepin (89.6%).

Step 2) : A suspension of 11-(1,4-dioxo-8-azaspiro[4,5]decane-8-yl)-2-bromo-6,11-dihydrodibenz[b,e]oxepin (5.5g, 13.2mmol) in 4N HCl was heated at 60-70°C for 30 minutes. Then ethanol was added to the mixture. The mixture was heated at 60-70°C for 1.5 hours. After ethanol was evaporated, the reaction mixture was made alkaline with 50% NaOH solution, then extracted with ethyl acetate and chloroform. The organic layer was washed with water, dried ( $\text{MgSO}_4$ ) and concentrated to give 11-(4-oxopiperidin-1-yl)-2-bromo-6,11-dihydrodibenz[b,e]oxepin (100%) : mp 196-200°C.

Step 3) : A suspension of  $\text{NH}_2\text{OHHCl}$  (1.22g, 17.5mmol) in ethanol

- (15ml) was added to the solution of 11-(4-oxopiperidin-1-yl)-2-bromo-6,11-dihydro-dibenz[b,e]oxepin (6.5g, 17.5 mmol) in ethanol (100ml) under refluxing. The reaction mixture was refluxed for 1 hour, then concentrated. The residue was suspended with saturated NaHCO<sub>3</sub> solution and then extracted with ethyl acetate.
- 5 The extract was washed with water, dried (MgSO<sub>4</sub>) and concentrated to give 11-(4-hydroxyiminopiperidin-1-yl)-2-bromo-6,11-dihydrodibenz[b,e]oxepin (100%) : mp 223-225°C.

- Step 4) : LiAlH<sub>4</sub> (0.14g, 3.7mmol) was added to a solution of 11-(4-hydroxyiminopiperidin-1-yl)-2-bromo-6,11-dihydrodibenz[b,e]oxepin (1.5g, 3.7mmol) in dry THF (50ml) under nitrogen atmosphere. The reaction mixture
- 10 was heated at 60-70°C for 3 hours. After cooled at 0°C, the reaction mixture was hydrolyzed with water and diluted with ether, then filtered. The filtrate was concentrated to give 11-(4-aminopiperidin-1-yl)-2-bromo-6,11-dihydrodibenz[b,e]oxepin (69.1%) : mp 142-144°C.

15 **PREPARATION 9**

**2-[2-(4-Aminopiperidin-1-yl)ethyl]thio-4,5-diphenylimidazole**

- Step 1) : 1-Bromo-2-chloroethane (10.0g, 0.07mmol) was added by portions to a solution of 1,4-dioxo-8-azaspiro[4,5]decane (1.0g, 7.0mmol) and Et 3N (0.7g, 7.0mmol) in acetonitrile (10ml) at 0°C. The mixture was stirred at 0°C
- 20 for 48 hours. poured into ethyl acetate and washed with water. The organic layer was dried (MgSO<sub>4</sub>) and concentrated to give 8-(2-chloroethyl)-1,4-dioxo-8-azaspiro-[4,5]decane (0.914g, 63.5%) as a solid product.

- Step 2) : NaH(0.213g, 8.8mmol) was added to a suspension of 4,5-diphenyl-2-imidazoethiol (1.12g, 4.4mmol) in THF (30ml). The mixture was
- 25 refluxed for 1 hour. To the reaction mixture, 8-(2-chloroethyl)-1,4-dioxo-8-azaspiro[4,5]decane (0.914g, 4.4mmol) was added at 0°C under stirring and refluxed 24 hours and then concentrated. The residue was poured into water and extracted with ethyl acetate. The organic layer was dried (MgSO<sub>4</sub>) and concentrated.

The precipitate was recrystallized (toluene) to give 2-[2-(1,4-dioxo-8-azaspiro[4,5]decane-8-yl)ethyl]thio-4,5-diphenylimidazole (0.970g, 52.3%).

Step 3) : A suspension of 2-[2-(1,4-dioxo-8-azaspiro[4,5]decane-8-yl)ethyl]thio-4,5-diphenylimidazole (0.86 g, 2.0 mmol) in concentrated HCl (20 ml) was heated at 60°C for 2 hours. The reaction mixture was made basic with 10% NaOH solution and extracted with ethyl acetate. The organic layer was dried (MgSO<sub>4</sub>) and concentrated to give 2-[2-(4-oxopiperidin-1-yl)ethyl]thio-4,5-diphenylimidazole (0.75g, 98.7%) as a clear oil.

Step 4) : Sodium cyanoborohydride (0.06g, 9.5mmol) was added to solution of 2-[2-(4-oxopiperidin-1-yl)ethyl]thio-4,5-diphenylimidazole (0.34g, 0.91mmol), powdered 3A molecular sieves (0.268g) and ammonium acetate (0.73g, 9.5mmol) in methanol (10ml). The mixture was stirred at room temperature under nitrogen atmosphere for 65 hours and then filtered and washed with methanol. The filtrate was concentrated. The residue was dissolved in 10% NaOH solution and ethyl acetate. The organic layer was washed with water and saturated NaCl solution, dried (MgSO<sub>4</sub>) and concentrated. The residue was purified by column chromatography on silica gel (0.8% NH<sub>4</sub>OH in chloroform/methanol) to give 2-[2-(4-aminopiperidin-1-yl)ethyl]thio-4,5-diphenylimidazole (172mg, 49.9%) as a pale yellow oil.

## 20 PREPARATION 10

### 2-(2-Aminoethylthio)-4,5-diphenylimidazole

60 % NaH in oil (0.91g, 22.8mmol) was added to a suspension of 4,5-diphenyl-2-imidazolethiol (2.5g, 9.9mmol) in dry THF (80ml) at room temperature under stirring. After 15 minutes, 2-bromoethylamine hydrobromide (2.0g, 9.9mmol) was added to the mixture. The reaction mixture was refluxed for 1 hour, then poured into water (500ml) and extracted with ethyl acetate. The extract was dried (MgSO<sub>4</sub>) and concentrated. The residue was recrystallized (toluene) to give 2-(2-aminoethylthio)-4,5-diphenylimidazole (51.3%) : mp 152-154°C.

**PREPARATION 11****1-(2-Aminoethyl)-4,5-diphenylimidazole**

Step 1) : A solution of 4,5-diphenylimidazole (2.5g, 11.3mmol) in dry DMF (20ml) was added to a suspension of NaH (0.33g, 13.8mmol) in dry DMF (5ml) at 50°C under nitrogen atmosphere. The reaction mixture was heated at 60°C for 2 hours. After heating, the mixture was added dropwise to a solution of 1-bromo-2-chloroethane (4.9g, 33.9mmol) in dry DMF (30ml) over 1 hour at 50°C. The reaction mixture was heated continuously at 40°C for 5 hours, then poured into water and extracted with ethyl acetate. The organic layer was washed with water, dried (MgSO<sub>4</sub>) and concentrated. The precipitates were filtered off. The filtrate was concentrated. The residue was purified by column chromatography on silica gel (ethyl acetate and hexane) to give 1-(2-chloroethyl)-4,5-diphenylimidazole (17.7%).

Step 2) : A mixture of potassium phthalimide (0.21g, 1.1mmol) and 1-(2-chloroethyl)-4,5-diphenylimidazole (0.32g, 1.1mmol) in dry DMF (10ml) was heated at 60-70°C for 6 hours. The reaction mixture was cooled, diluted with chloroform, poured into water and extracted with chloroform. The organic layer was dried (MgSO<sub>4</sub>) and concentrated. The residue was purified by column chromatography on silica gel (40% ethyl acetate in chloroform) to give 1-(2-phthalimidoethyl)-4,5-diphenylimidazole (73.0%).

Step 3) : 80% Hydrazine monohydrate (0.062ml, 1.3mmol) was added to a solution of 1-(2-phthalimidoethyl)-4,5-diphenylimidazole (0.32g, 0.8mmol) in methanol (20ml) under refluxing. The reaction mixture was refluxed for 1 hour, then cooled. The mixture was made acidic slightly with 6N HCl and then filtered to remove phthalhydrazide. The filtrate was concentrated and then the residue was suspended in 2N NaOH. The suspended mixture was extracted with chloroform. The organic layer was washed with brine, dried (MgSO<sub>4</sub>) and concentrated. The precipitates were recrystallized (ethyl acetate / hexane) to give 1-(2-aminoethyl)-4,5-diphenylimidazole (88.1%) : mp 96-98°C.

**PREPARATION 12****2-Amino-5-dimethylamino-N-[(1-diphenylmethylpiperidin-4-yl)methyl]-benzamide**

Step 1) : A mixture of 5-dimethylamino-2-nitrobenzoic acid [J. Med. Chem., 24, 742 (1981)] (9.0g, 40mmol), 4-aminomethyl-1-diphenylmethylpiperidine (12.0g, 40mmol), 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (WSC) (8.0g, 40mmol) and 4-dimethylaminopyridine (DMAP) (5g, 40mmol) in dichloromethane (400ml) was stirred at 0°C for 1 hour, then at room temperature for 3 days. The reaction mixture was washed with 1N HCl, then water. The organic layer was dried (MgSO<sub>4</sub>) and concentrated. The residue was purified by column chromatography on silica gel (5% methanol in dichloromethane) to give 5-dimethylamino-2-nitro-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide (47%) as yellow solid : mp 200°C.

Step 2) : A mixture of 5-dimethylamino-2-nitro-N-[(1-diphenylmethylpiperidin-4-yl)-methyl] benzamide (2.4g, 5mmol) and Raney Ni in methanol (50ml) was hydrogenated at room temperature under stirring under 50 psi hydrogen pressure for 2 hours and then filtered. The filtrate was concentrated to give 2-amino-5-dimethylamino-N-[(1-diphenylmethylpiperidin-4-yl)-methyl]benzamide (2.2g, 100%).

**20 PREPARATION 13****2-Amino-5-dimethylamino-N-(1-diphenylmethylpiperidin-4-yl)benzamide**

In a similar manner to that of Preparation 12, but replacing 4-aminomethyl-1-diphenylmethylpiperidine with 4-amino-1-diphenylmethylpiperidine (US Patent No. 4,267,318), 2-amino-5-dimethylamino-N-(1-diphenylmethylpiperidin-4-yl)benzamide was prepared.

**PREPARATION 14****2-Amino-5-fluoro-N-(1-diphenylmethylpiperidin-4-yl)benzamide**

In a similar manner to that of Preparation 12, 2-amino-5-fluoro-N-(1-diphenylmethylpiperidin-4-yl)benzamide was prepared from 5-fluoro-2-nitro-

benzoic acid and 4-amino-1-diphenylmethylpiperidine.

#### PREPARATION 15

##### 2-Amino-3-dimethylamino-N-(1-diphenylmethylpiperidin-4-yl)benzamide

Step 1) : In a similar manner to Preparation 12 Step 1), 3-chloro-2-nitro-N-(1-diphenylmethylpiperidin-4-yl)benzamide was prepared from 3-chloro-2-nitrobenzoic acid and 4-amino-1-diphenylmethylpiperidine.

Step 2) : A solution of 3-chloro-2-nitro-N-(1-diphenylmethylpiperidin-4-yl)benzamide (13.5g, 30mmol) and 40 % dimethylamine (20ml) in DMF (60ml) was heated at 130°C for 15.5 hours in a sealed tube. The mixture was poured into water and extracted with ether. The organic layer was washed with water, dried (MgSO<sub>4</sub>) and concentrated. The residue was recrystallized (ethyl acetate / hexane) to give 3-dimethylamino-2-nitro-N-(1-diphenylmethyl piperidin-4-yl)benzamide (88.5%) : mp 176°C.

Step 3) : In a similar manner to Preparation 12 Step 2), but replacing 5-dimethylamino-2-nitro-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide with 3-dimethylamino-2-nitro-N-(1-diphenylmethylpiperidin-4-yl)benzamide, 2-amino-3-dimethylamino-N-(1-diphenylmethylpiperidin-4-yl)benzamide was prepared.

#### PREPARATION 16

##### 2-Amino-3,5-dimethoxy-N-(1-diphenylmethylpiperidin-4-yl)benzamide

Step 1) : A solution of SOCl<sub>2</sub> (0.5ml, 6.6mmol) in chloroform (10ml) was added dropwise to a solution of 3,5-dimethoxy-2-nitrobenzoic acid [ Bull. Soc. Chim. Fr., 127, 258 (1990)] (1.0g, 4.4mmol) and a catalytic amount of DMF in chloroform (20ml) at room temperature. The reaction mixture was refluxed for 1 hour and then concentrated. The residue was dissolved in THF(10ml). The THF solution was added dropwise to a solution of 4-amino-1-diphenylmethylpiperidine (1.2g, 4.4mmol) and triethylamine (0.5ml, 6.6mmol) in THF (20ml) at 5°C. The mixture was stirred at room temperature for 1 hour and then concentrated. The residue was dissolved in ethyl acetate and washed with water. The organic layer

was dried ( $\text{MgSO}_4$ ) and concentrated. The residue was purified by column chromatography on silica gel (10% ethyl acetate in dichloromethane) to give 3,5-dimethoxy-2-nitro-N-(1-diphenylmethylpiperidin-4-yl)benzamide (81.0%) : mp 148-150°C.

5                    Step 2) : In a similar manner to that of Preparation 12 Step 2), but replacing 5-dimethylamino-2-nitro-N-(1-diphenylmethylpiperidin-4-yl)methylbenzamide with 3,5-dimethoxy-2-nitro-N-(1-diphenylmethylpiperidin-4-yl)benzamide. 2-amino-3,5-dimethoxy-N-(1-diphenylmethyl-piperidin-4-yl)benzamide was prepared : 100 %.

#### 10    **PREPARATION 17**

##### **2-Amino-N-(2,6-diisopropylphenyl)benzamide**

Step 1) : In a similar manner to that of Preparation 16 Step 1), 2-nitro-N-(2,6-diisopropylphenyl)benzamide was prepared from 2-nitrobenzoyl chloride and 2,6-diisopropylaniline : 67.9 %, mp 119-121°C.

15                    Step 2) : Zinc powder (7.81 g, 119 mmol) was added slowly to a solution of 2-nitro-N-(2,6-diisopropylphenyl)benzamide (2.0g, 6.3mmol) in acetic acid (38.3ml) below 10°C. The mixture was stirred for 2 hours at room temperature. The excess reagent was filtered off and the filtrate was neutralized with 10% NaOH solution. The mixture was extracted with ethyl acetate. The organic layer was dried ( $\text{MgSO}_4$ ) and concentrated. The residue was recrystallized (ethyl acetate / hexane) to give 2-amino-N-(2,6-diisopropylphenyl)benzamide (77.1 %) : mp 207-209°C.

#### 20    **PREPARATION 18**

##### **2-Amino-5-hydroxy-N-(3,3-diphenylpropyl)benzamide**

25                    In a similar manner to that of Preparation 12 Step 2), but replacing 5-dimethylamino-2-nitro-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide with 5-benzyloxy-2-nitro-N-(3,3-diphenylpropyl)benzamide [J. Med. Chem. 31, 2136 (1988)], 2-amino-5-hydroxy-N-(3,3-diphenylpropyl)benzamide was prepared.

## PREPARATION 19

2-Amino-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide and its analogue compounds of the formula(2)

A solution of 4-aminomethyl-1-diphenylmethylpiperidine (2.5g, 9.15mmol) in dichloromethane (10ml) was added to a suspension of isatoic anhydride (1.0g, 6.1mmol) in dichloromethane (25ml) at room temperature. The reaction mixture was stirred for 1 hour and then poured into chloroform and washed with 5% NaHCO<sub>3</sub> solution. The organic layer was concentrated. The residue was dissolved in dichloromethane (25ml) and poured into hexane (400ml) to give 2-amino-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide as precipitate (100 %) : mp 153-154°C.

In a similar manner, but replacing the 4-aminomethyl-1-diphenylmethylpiperidine and the isatoic anhydride with other appropriately substituted amine and other appropriately substituted isatoic anhydride respectively, the following compounds were prepared and identified.

2-amino-N-(1-diphenylmethylpiperidin-4-yl)benzamide;

2-amino-3-isopropyl-N-(1-diphenylmethylpiperidin-4-yl)benzamide;

2-amino-5-nitro-N-(1-diphenylmethylpiperidin-4-yl)benzamide;

2-amino-N-[2-(1-diphenylmethylpiperidin-4-yl)ethyl]benzamide;

2-amino-N-[3-(1-diphenylmethylpiperidin-4-yl)propyl]benzamide;

2-amino-N-(1-benzylpiperidin-4-yl)benzamide;

2-amino-N-[3-(1-diphenylmethylpyrrolidin-3-yl)propyl]benzamide;

2-amino-N-(pyridin-3-yl)benzamide;

2-amino-N-(pyridin-2-yl)benzamide;

1-(2-aminobenzoyl)-4-diphenylmethylpiperazine;

1-(2-aminobenzoyl)-4-(2-methoxyphenyl)piperazine;

1-(2-aminobenzoyl)-4-diphenylmethylhomopiperazine;

1-(2-aminobenzoyl)-4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-piperazine.



**PREPARATION 20****2-Amino-N-methyl-N-[(1-diphenylmethylpiperidin-4-yl)-methyl]benzamide**

Step 1) : To a cooled solution (0-5°C) of 4-aminomethyl-1-diphenylmethylpiperidine (3.0g, 0.01mol) in formic acid (7.5ml), acetic anhydride (6ml) was added and the reaction mixture was stirred at room temperature for 17 hours. An aqueous NaOH solution was added to adjust the mixture to pH 12 and the mixture was extracted with ether. The organic layer was washed with water and brine, dried (MgSO<sub>4</sub>) and concentrated. The residue was recrystallized (diisopropyl ether) to give 4-(N-formylamino)methyl-1-diphenylmethylpiperidine (2.9g, 88%); mp 125°C.

Step 2) : In a similar manner to that of Preparation 1 step2), 4-(N-formylamino)methyl-1-diphenylmethylpiperidine was reduced by LiAlH<sub>4</sub> to give 4-(N-methylamino)methyl-1-diphenylmethylpiperidine; yield 100%.

Step 3) : A solution of 4-(N-methylamino)methyl-1-diphenylmethylpiperidine (1.8g, 6.0mmol), isatoic anhydride (0.9g, 5.5mmol) and 4-dimethylaminopyridine (0.74g) in DMF (25ml) was stirred at room temperature for 2 hours. The reaction mixture was poured into 1% NaHCO<sub>3</sub> solution and extracted with ethyl acetate. The organic layer was washed with water, dried and concentrated. The residue was purified by column chromatography on silica gel (ethyl acetate and hexane) to give 2-amino-N-methyl-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide (1.5g, 67%).

**PREPARATION 21****3-Aminomethyl-1-diphenylmethylpiperidine**

Step 1) : A solution of bromodiphenylmethane (48.2g, 195mmol) in DMSO (30ml) was added dropwise to a solution of nipecotamide (25g, 195mmol) and K<sub>2</sub>CO<sub>3</sub> (27g, 195mmol) in CH<sub>3</sub>CN (100ml) and DMSO (50ml) under stirring and cooling in an ice-bath for 1 hour. After the addition was complete, the mixture was stirred overnight at room temperature. The insoluble precipitates were filtered off and then the filtrate was evaporated. To the residue was added H<sub>2</sub>O and

AcOEt. and agitated. The organic layer was washed with H<sub>2</sub>O, dried over MgSO<sub>4</sub> and evaporated to give 1-diphenylmethylpiperidin-3-carboxamide. 33g (57.5%) : mp 86-87°C.

Step 2) : To a suspension of LiAlH<sub>4</sub> (10g, 263mmol) in THF (100ml)  
5 was added dropwise a solution of 1-diphenylmethylpiperidin-3-carboxamide (32g, 109mmol) in THF (130ml) for 40 mins under stirring and cooling in an ice-bath. After the addition was complete, the mixture was refluxed for 2 hours and then cooled. To the resulting mixture, 15% NaOH aqueous solution and H<sub>2</sub>O were added dropwise in order, and the insoluble materials were filtered off. The filtrate  
10 was dried over MgSO<sub>4</sub> and evaporated. The residue was purified by column chromatography on silica gel to give 3-aminomethyl-1-diphenylmethylpiperidine as a colorless oil. 23g (75.5%).

#### PREPARATION 22

4-Aminomethyl-1-(dibenzosuberan-5-yl)piperidine

15 4-Aminomethyl-1-(biphenyl-2-methyl)piperidine

4-Aminomethyl-1-(biphenyl-4-methyl)piperidine

4-Aminomethyl-1-[bis(4-fluorophenyl)methyl]piperidine

4-Aminomethyl-1-[bis(4-chlorophenyl)methyl]piperidine

4-Aminomethyl-1-[bis(4-methoxyphenyl)methyl]piperidine

20 In a similar manner to that of Preparation 1, but replacing bromodiphenylmethane with 5-chlorodibenzosuberane, 2-(bromomethyl)biphenyl, 4-(chloromethyl)biphenyl, chloro-bis(4-fluorophenyl)methane, chloro-bis(4-chlorophenyl)methane and chloro-bis(4-methoxyphenyl)methane, the above-mentioned amine derivatives were prepared.

#### 25 PREPARATION 23

4-(1-Amino-1-methyl)ethyl-1-diphenylmethylpiperidine

Step 1) : A solution of 1-diphenylmethylpiperidine-4-carboxamide (14.79 g, 50mmol) in POCl<sub>3</sub> (300 ml) was refluxed for 3.5 hours. The reaction mixture was concentrated under vacuum. The residue was dissolved into the

mixture of sat.  $\text{NaHCO}_3$  aq. solution and  $\text{AcOEt}$ . After separation, the aqueous layer was extracted with  $\text{AcOEt}$ . The combined organic layer was washed with  $\text{H}_2\text{O}$  and brine, dried over  $\text{MgSO}_4$  and then concentrated. The residue was recrystallized from iso- $\text{PrOH}$  to give 4-cyano-1-diphenylmethylpiperidine, 12.36 g (89%) : mp 219-230 °C.

Step 2):  $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$  (39.18g, 105mmol) was dried with stirring at 150°C under vacuum for 2 hours, and then THF (200 ml) was added to make suspension.  $\text{MeLi}$  (1.4N solution in  $\text{Et}_2\text{O}$  : 75 ml, 105mmol) was added dropwise at the temperature under -70°C. The mixture was stirred at -75°C for 1 hour. A solution of 4-cyano-1-diphenylmethylpiperidine (9.69 g) in THF (50 ml) was added dropwise at the same temperature. The mixture was allowed to warm to room temperature and stirred for 2 hours. The mixture was filtered, and the filtrate was concentrated. The residue was dissolved into the mixture of  $\text{H}_2\text{O}$  and  $\text{CH}_2\text{Cl}_2$ . After separation, the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$ . The combined organic layer was washed with  $\text{H}_2\text{O}$  and brine, dried over  $\text{MgSO}_4$ , and then concentrated. The residue was chromatographed on silica gel (10%  $\text{MeOH}$  in  $\text{AcOEt} + \text{NH}_4\text{OH}$ ) to give 4-(1-amino-1-methyl)ethyl-1-diphenylmethylpiperidine. 6.69g (62%) : mp 110-115 °C.

#### PREPARATION 24

20 2-Amino-5-dimethylamino-N-[(1-diphenylmethylpiperidin-4-yl)methyl]-benzamide

Step 1) : Conc.  $\text{HNO}_3$  (25ml) was added dropwise to a solution of 3-fluorobenzoic acid (25g, 178mmol) in conc.  $\text{H}_2\text{SO}_4$  (190ml) under cooling in an ice-bath and stirring for 30 mins. After the addition was complete, the mixture was stirred at 0°C and at room temperature for each 30 mins. The resulting solution was poured into an ice water and extracted with  $\text{AcOEt}$ . The extract was washed with brine, dried over  $\text{MgSO}_4$  and evaporated to give 5-fluoro-2-nitrobenzoic acid as yellow powder, 32.1g (97.2%) : mp 141-142°C.

Step 2) : A mixture of 5-fluoro-2-nitrobenzoic acid (15g, 81mmol),

thionyl chloride (20g, 168mmol) and DMF (10drops) in  $\text{CHCl}_3$  (120ml) was refluxed for 6 hours and then the resulting solution was evaporated to give colorless paste. This paste was used in the next step without purification.

Step 3) : To a solution of 4-aminomethyl-1-diphenylmethylpiperidine  
5 (23g, 82 mmol) and triethylamine (22g, 217mmol) in THF (140ml) was added dropwise a solution of the above-obtained paste in THF (60ml) under stirring and cooling in an ice-bath, and then the mixture was stirred for additional 20 hours at room temperature. The insoluble precipitates were filtered off and the filtrate was evaporated to give 5-fluoro-2-nitro-N-[(1-di-phenylmethylpiperidin-4-yl)-  
10 methyl]benzamide as pale yellow powders. 33.5 g (92.4%) :mp 164-166°C.

Step 4) : A mixture of 5-fluoro-2-nitro-N-[(1-diphenylmethylpipe-  
ridin-4-yl)-methyl] benzamide (13.4g, 30mmol) and 2.0M MeOH solution of dimethylamine (45ml, 90mmol) in THF (100ml) was refluxed for 22 hours. The resulting solution was evaporated to give 5-dimethylamino-2-nitro-N-[(1-  
15 diphenylmethylpiperidin-4-yl)methyl]benzamide as yellow powders, 14.1 g (99.6%) .

Step 5) : To a solution of 5-dimethylamino-2-nitro-N-[(1-diphenyl-  
methylpiperidin-4-yl)methyl]benzamide (3.55g, 7.5mmol) in a mixture of MeOH/  
AcOEt (50ml/50ml) was added  $\text{PtO}_2$  (100mg). The suspended mixture was  
20 agitated under  $\text{H}_2$  atmosphere ( $3\text{kg}/\text{cm}^2$ ) for 3 hours. The mixture was filtered, and the filtrate was concentrated under vacuum. The residue was triturated with  $\text{Et}_2\text{O}$  to give 2-amino-5-dimethylamino-N-[(1-diphenylmethylpipe-  
ridin-4-yl)methyl]-  
benzamide as a colorless powder product, 3.0g (92.0%).

#### PREPARATION 25

25 2-Amino-5-(N-tert-butoxycarbonyl-N-methyl)amino-N-[(1-diphenylmethyl-  
piperidin-4-yl)methyl]benzamide

Step 1) : A mixture of 5-fluoro-2-nitro-N-[(1-diphenylmethylpipe-  
ridin-4-yl)methyl]benzamide (2.68g, 6mmol) and 40% methylamine in MeOH  
(5ml, 64mmol) in DMF (30ml) was heated in a sealed tube at 180°C for 7 hours.

After cooling, the reaction mixture was poured into H<sub>2</sub>O and extracted with AcOEt. The extract was washed with H<sub>2</sub>O, dried over MgSO<sub>4</sub> and evaporated, followed by crystallization from EtOH to give 5-methylamino-2-nitro-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide. 2.28g (83%) : mp 185°C.

5           Step 2) : A mixture of 5-methylamino-2-nitro-N-[(1-diphenylmethylpiperidin-4-yl)methyl] benzamide (1.1g, 2.4mmol), di-tert-butyl dicarbonate (5.3g, 24.3mmol), triethylamine (5 drops) and DMF (1ml) was heated at 180°C overnight. After cooling, the reaction mixture was dissolved in CHCl<sub>3</sub> and the solution was washed with H<sub>2</sub>O, dried over MgSO<sub>4</sub> and evaporated. The residue  
10       was purified by column chromatography on silica gel to give 5-(N-tert-butoxycarbonyl-N-methyl)amino-2-nitro-N-[(1-diphenylmethylpiperidin-4-yl)-methyl]benzamide. 840mg (62.5%) : mp 167-168°C.

          Step 3) : A mixture of 5-(N-tert-butoxycarbonyl-N-methyl)amino-2-nitro-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide (650mg, 1.16mmol)  
15       and PtO<sub>2</sub> (110mg) in MeOH (50ml) was agitated under H<sub>2</sub> atmosphere (3kg/cm<sup>2</sup>) at room temperature for 5 hours. The catalysts were filtered off and the filtrate was evaporated to give 2-amino-5-(N-tert-butoxycarbonyl-N-methyl)amino-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide as colorless powders. 550mg (89.4%) : mp 219-221°C (decomp.).

## 20   **PREPARATION 26**

### **2-Amino-5-methylthio-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide**

          Step 1) : To a solution of 5-fluoro-2-nitro-N-[(1-diphenylmethylpiperidin-4-yl)methyl] benzamide (2.0g, 4.46mmol) in DMF (10ml) was added  
25       dropwise a solution of sodium thiomethoxide (343mg, 4.9mmol) in DMF (10ml) under stirring at room temperature. After the mixture was stirred overnight, an additional sodium thiomethoxide (34mg, 0.49mmol) was added to the mixture. The reaction mixture was diluted with AcOEt and washed twice with H<sub>2</sub>O. The organic layer was dried over MgSO<sub>4</sub> and evaporated to give 5-methylthio-2-nitro-

N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide as colorless powders. 1.7g (80%) : mp 179-181°C.

Step 2) : A mixture of 5-methylthio-2-nitro-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide (500mg, 1.05mmol), Fe powder (587mg, 1.05 mmol), conc.HCl (0.05ml), H<sub>2</sub>O (8 ml) and EtOH (35ml) was refluxed overnight. The insoluble precipitates were filtered off and then the filtrate was evaporated to give 2-amino-5-methylthio-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide as colorless powder. 450mg (96%) : mp 156-157°C.

#### PREPARATION 27

##### 2-Amino-5-hydroxy-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide

Step 1) : A solution of 5-hydroxyanthranilic acid (500mg, 3.26mmol) and triphosgene (1.45g, 4.9mmol) in 1,4-dioxane (20ml) was refluxed overnight. The reaction mixture was poured into H<sub>2</sub>O (30ml), and then the precipitates were filtered and dried to give 6-hydroxy-1.2-dihydro-4H-3.1-benzoxazin-2.4-dione, 360mg (62%).

Step 2) : A mixture of 6-hydroxy-1.2-dihydro-4H-3.1-benzoxazin-2.4-dione (360mg, 2mmol) and 4-aminomethyl-1-diphenylmethylpiperidine (420mg, 1.5mmol) in DMSO (5ml) was stirred for 3 hours at room temperature. The reaction mixture was diluted with AcOEt and washed twice with brine. The organic layer was dried over MgSO<sub>4</sub> and evaporated, and then the residue was purified by column chromatography on silica gel to give 2-amino-5-hydroxy-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide. 520mg (63%).

#### PREPARATION 28

##### 2-Amino-5-nitro-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide

4-Dimethylaminopyridine (122mg, 1.0mmol) was added to a solution of 6-nitro-1.2-dihydro-4H-3.1-benzoxazin-2.4-dione (prepared by nitration of isatoic anhydride) (2.0g, 9.6mmol) in DMF (15ml) and stirred for 5 mins.

To this solution was added 4-aminomethyl-1-diphenylmethylpiperidine (2.7g, 9.6mmol) and stirred for 5 hours at room temperature. The

reaction mixture was diluted with AcOEt (50ml) and H<sub>2</sub>O (50ml). The aqueous layer was extracted with AcOEt. The combined AcOEt layer was washed twice with brine, dried over MgSO<sub>4</sub> and evaporated. The residue was purified by column chromatography on silica gel to give 2-amino-5-nitro-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide, 2.47g (58%).

#### PREPARATION 29

##### 2-Amino-5-isopropyl-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide

Step 1) : 30% H<sub>2</sub>O<sub>2</sub> (6ml) was added to a solution of 5-isopropyl-1H-indole-2,3-dione [ J. Med. Chem., 19, 391(1976)] (4.0g, 21.1mmol) in 1N-NaOH (15ml) at 5°C. The mixture was stirred for 3 hours at room temperature and then poured into H<sub>2</sub>O and acidified. The precipitates were filtered to give 5-isopropylanthranilic acid, 2.6g (68.6%) : mp 93-95°C.

Step 2) : (BOC)<sub>2</sub>O (2.5g, 14.3mmol) was added to a solution of 5-isopropyl-anthranilic acid (2.5g, 13.9mmol) in t-BuOH. The mixture was stirred for 18 hours at room temperature and then poured into H<sub>2</sub>O and extracted with AcOEt. The extract was washed with H<sub>2</sub>O, dried over MgSO<sub>4</sub> and evaporated. The residue was purified by column chromatography on silica gel to give 5-isopropyl-N-tert-butoxycarbonylanthranilic acid, 2.5g (63.4%) : mp 175°C.

Step 3) : A mixture of 5-isopropyl-N-tert-butoxycarbonylanthranilic acid (1.0 g, 3.58mmol), 4-aminomethyl-1-diphenylmethylpiperidine (1.0g, 3.57mmol), triethylamine (0.37g, 3.66mmol) and DPPA (1.0g, 3.63mmol) in DMF was stirred at 0°C for 30 mins and at room temperature for 2 hours. The mixture was poured into H<sub>2</sub>O and extracted with AcOEt. The extract was washed with H<sub>2</sub>O, dried over MgSO<sub>4</sub> and evaporated and then the residue was purified by column chromatography on silica gel to give 2-(tert-butoxycarbonyl)amino-5-isopropyl-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide, 1.86g (96.4%) : mp 88-90°C.

Step 4) : A mixture of 2-(tert-butoxycarbonyl)amino-5-isopropyl-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide (1.86g, 3.43mmol) in TFA

(5ml) was stirred at 0°C for 30 mins and at room temperature for 30 mins. The mixture was poured into H<sub>2</sub>O, neutralized with 15% NaOH aq. solution and extracted with AcOEt. The extract was washed with H<sub>2</sub>O, dried over MgSO<sub>4</sub> and evaporated to give 2-amino-5-isopropyl-N-[(1-diphenylmethylpiperidin-4-yl)-methyl]benzamide, 1.49g (97.7%) : mp 114-116°C.

### PREPARATION 30

#### 2-Amino-4-chloro-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide

To a solution of 7-chloro-1,2-dihydro-4H-3,1-benzoxazin-2,4-dione (prepared by cyclization of N-benzoyloxycarbonyl-4-chloroanthranilic acid with phosphorus tribromide ) (1.0g, 5.06mmol) in DMF (18ml) was added 4-dimethylaminopyridine (62mg). After 5 mins of agitation at room temperature, 4-aminomethyl-1-diphenylmethylpiperidine (1.56g, 5.56mmol) was added to the solution and stirred for 5 hours. The reaction mixture was diluted with AcOEt, washed twice with H<sub>2</sub>O, dried over MgSO<sub>4</sub> and evaporated. The residue was purified by column chromatography on silica gel to give 2-amino-4-chloro-N-[(1-diphenylmethylpiperidin-4-yl)methyl] benzamide, 892mg (41%) : mp 161-162°C.

### PREPARATION 31

#### 2-Amino-6-dimethylamino-N-(1-diphenylmethylpiperidin-4-yl)benzamide

Step 1) : An ice cooled solution of bromine (2.5 ml, 48.5mmol) in 1N KOH aq.solution was added to the solution of 3-nitrophthalimide (9.66 g, 50mmol) in 1N KOH aq.solution (150 ml) followed by 1N KOH at 0. The mixture was refluxed for 1.5 hours. After cooling, the mixture was neutralized with 2N HCl and stirred at 0 to precipitate 2-amino-6-nitrobenzoic acid, 6.23g (68%) : mp 190 °C

Step 2) : A mixture of 2-amino-6-nitrobenzoic acid (3.64g, 20mmol), 4-amino-1-diphenylmethylpiperidine (5.33g, 20mmol), EDCI (4.00g, 21mmol) and DMAP (2.45g, 20mmol) in CH<sub>2</sub>Cl<sub>2</sub> (60ml) was stirred at room temperature for 56.5 hours. The reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>, washed with H<sub>2</sub>O and brine. The organic layer was dried over MgSO<sub>4</sub> and concentrated under



vacuum. The residue was purified with chromatography on SiO<sub>2</sub> (30-50% AcOEt in hexane) and recrystallized from toluene to obtain 2-amino-6-nitro-N-(1-diphenyl-methylpiperidin-4-yl)benzamide. 2.33g (27%) : mp 217 °C.

Step 3) : A suspension of 2-amino-6-nitro-N-(1-diphenylmethyl-  
5 piperidin-4-yl) benzamide (2.00g, 4.4mmol) and NaBH<sub>4</sub> (1.25g, 33mmol) in THF (35ml) was added slowly to an ice cooled mixture of 37% HCHO aq. solution (2.15ml, 26.5mmol) and 3M H<sub>2</sub>SO<sub>4</sub> aq. solution (3.7ml) at 0. The mixture was stirred at 0 for 1.5 hours, and then made strongly alkaline with NaOH aq. solution and extracted with Et<sub>2</sub>O. The organic layer was washed with H<sub>2</sub>O and brine, dried  
10 over MgSO<sub>4</sub> and concentrated under vacuum. The residue was recrystallized from a mixture of cyclohexane and AcOEt to obtain 2-dimethylamino-6-nitro-N-(1-diphenylmethylpiperidin-4-yl)benzamide 2.07g (97%) : mp 122 °C.

Step 4) : A mixture of 2-dimethylamino-6-nitro-N-(1-diphenyl-  
methylpiperidin-4-yl)benzamide (1.60g, 3.5mmol) and Raney Nickel in EtOH  
15 (75ml) was stirred under H<sub>2</sub> at room temperature for 4 hours. The mixture was filtered, and the filtrate was concentrated under vacuum to obtain 2-amino-6-dimethylamino-N-(1-diphenylmethylpiperidin-4-yl) benzamide. 1.42g (95%).

## PREPARATION 32

### 2-Amino-4-dimethylamino-N-(1-diphenylmethylpiperidin-4-yl)benzamide

20 Step 1) : A hot solution of sodium polysulfate was added dropwise to the solution of 2,4-dinitrobenzoic acid (8.9g, 42mmol) in boiling water (400ml). The mixture was refluxed for 1 hour.

After cooling, conc. HCl was added to the mixture to adjust the pH value of 2. And then, reflux was continued for 1 hour to remove excess Na polysulfate. The mixture was cooled, made alkaline with 40% NaOH aq. solution  
25 to adjust the pH value of 10 and filtered. The solids was washed with 5% Na<sub>2</sub>CO<sub>3</sub> aq. solution. The filtrate was acidified with conc. HCl to adjust the pH value of 5 and treated with AcOH (50ml) to obtain a precipitate. The recrystallization from H<sub>2</sub>O afforded 4-amino-2-nitrobenzoic acid 4.2g (55%) : mp 230 °C.

Step 2) : A suspension of 4-amino-2-nitrobenzoic acid (0.80g, 4.4mmol) and NaBH<sub>4</sub> (1.25g, 33mmol) in THF (35ml) was added slowly to an ice cooled mixture of 37% HCHO aq. solution (2.15ml, 26.5mmol) and 3M H<sub>2</sub>SO<sub>4</sub> (3.7ml) aq. solution at 0. The mixture was stirred at 0 for 1.5 hours, and then  
5 neutralized with NaOH aq. solution to adjust the pH value of 3 and extracted with Et<sub>2</sub>O. The organic layer was washed with H<sub>2</sub>O and brine, dried over MgSO<sub>4</sub> and concentrated under vacuum. The residue was recrystallized from MeOH to obtain 4-dimethylamino-2-nitrobenzoic acid 0.74g (80%).

Step 3) : The mixture of 4-dimethylamino-2-nitrobenzoic acid (4.20g, 20 mmol), 4-amino-1-diphenylmethylpiperidine (5.33g, 20mmol), EDCI (4.00g, 21mmol) and DMAP (2.45g, 20mmol) in CH<sub>2</sub>Cl<sub>2</sub> (60ml) was stirred at room  
10 temperature for 17.5 hours. The reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>, washed with H<sub>2</sub>O and brine. The organic layer was dried over MgSO<sub>4</sub> and concentrated under vacuum. The residue was purified with chromatography on SiO<sub>2</sub> (50% AcOEt in hexane) and recrystallized from AcOEt to obtain 4-  
15 dimethylamino-2-nitro-N-(1-diphenylmethylpiperidin-4-yl)benzamide. 5.44g (59 %) : mp 183 °C.

Step 4) : The mixture of 4-dimethylamino-2-nitro-N-(1-diphenylmethylpiperidin-4-yl)-benzamide (1.60g, 3.5mmol) and Raney Nickel in EtOH (75ml)  
20 was stirred under H<sub>2</sub> at room temperature for 4 hours. The mixture was filtered, and the filtrate was concentrated under vacuum. The residue was purified with chromatography on silica gel (30-50% AcOEt in hexane) and recrystallized from diisopropyl ether to obtain 2-amino-4-dimethylamino-N-(1-diphenylmethylpiperidin-4-yl)benzamide 1.18g(79%) : mp 118 °C.

### 25 PREPARATION 33

#### 2-Amino-5-(N-acetyl-N-methyl)amino-N-[(1-diphenylmethylpiperidin-4-yl)-methyl]-benzamide

Step 1) : A mixture of 5-methylamino-2-nitro-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide (Preparation 24) (810mg, 1.77mmol) and acetic

anhydride (3g, 29.4mmol) was refluxed for 1.5 hours. To the reaction mixture was added MeOH and evaporated to give oil. This oil was triturated with Et<sub>2</sub>O to give 5-(N-acetyl-N-methyl)amino-2-nitro-N-[(1-diphenyl-methyl)piperidin-4-yl)methyl]benzamide. 470mg (53.2%) as pale yellow powders product. mp 175-176 °C.

5 Step 2) : A mixture of 5-(N-acetyl-N-methyl)amino-2-nitro-N-[(1-diphenylmethyl)piperidin-4-yl)methyl]benzamide (500mg, 1.0mmol) and PtO<sub>2</sub> (110mg) in MeOH (40ml) was stirred under H<sub>2</sub> atmosphere (3kg/cm<sup>2</sup>) at room temperature. The catalysts were filtered off and the filtrate was evaporated to give 2-amino-5-(N-acetyl-N-methyl)amino-N-[(1-diphenylmethyl)piperidin-4-yl)methyl]benzamide as a colorless powder product. That product was used in the next step without purification. mp 224-226 °C.

#### EXAMPLE 1

##### 2-(N'-n-Heptylureido)-5-dimethylamino-N-[(1-diphenylmethyl)piperidin-4-yl)methyl]- benzamide

15 A solution of phenyl chloroformate (0.7ml, 5mmol) in dichloromethane (5ml) was added dropwise to a solution of 2-amino-5-dimethylamino-N-[(1-diphenylmethyl)piperidin-4-yl)methyl]benzamide (2.2g, 5mmol) and NaHCO<sub>3</sub> (1.0g, 11.9mmol) in dichloromethane (50ml).

The reaction mixture was stirred at 0°C for 30 minutes and then  
20 poured into water and extracted with dichloromethane. The organic layer was dried (MgSO<sub>4</sub>) and concentrated to give 2-phenoxy-carbonylamino-5-dimethylamino-N-[(1-diphenylmethyl)piperidin-4-yl)methyl]benzamide.

n-Heptylamine (2.3g, 20.2mmol) was added to a solution of the carbamate described above in dichloromethane (50ml). The mixture was refluxed  
25 for 3 hours and then concentrated. The residue was purified by column chromatography on silica gel to give 2-(N'-n-heptylureido)-5-dimethylamino-N-[(1-diphenylmethyl)piperidin-4-yl)methyl]benzamide (1.8g, 62.0%) : mp 178-179°C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)ppm : 0.86 (3H, t), 1.14-1.47 (12H, m), 1.50-1.68 (3H, m), 1.79 (2H, t), 2.70-2.89 (8H, m), 2.97 (2H, dt), 3.14 (2H, t), 4.27 (1H, s),

6.78-6.90 (3H. m), 7.13-7.41 (10H. m), 7.85 (1H. d), 8.51 (1H. t), 9.17 (1H. s).

In a similar manner, the following compounds (Examples 2 to 26) were prepared from other appropriately substituted 2-amino-benzamides and other appropriately substituted amines which were described in braces : {} after title of these compounds.

#### EXAMPLE 2

2-(N'-n-Butylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide

{2-amino-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide and n-butylamine} : yield 80.2% ; mp 197-198°C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)ppm : 0.86 (3H. t), 1.24-1.83 (11H. m), 2.79 (2H. d), 3.02(2H. dd), 3.15 (2H. t), 4.27 (1H. s), 6.91 (1H. t), 7.13-7.41 (12H. m), 7.57 (1H. d), 8.21 (1H. d), 8.57 (1H. t), 9.92 (1H. s).

#### EXAMPLE 3

2-(N'-n-Pentylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide

{2-amino-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide and n-pentylamine} : yield 29.9% ; mp 178-180°C (EtOH); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)ppm : 0.86 (3H. t), 1.24-1.83 (13H. m), 2.79 (2H. d), 2.96 (2H. dd), 3.15 (2H. t), 4.26 (1H. s), 6.91 (1H. t), 7.13-7.41 (12H. m), 7.57 (1H. d), 8.22 (1H. d), 8.58 (1H. t), 9.93 (1H. s).

#### EXAMPLE 4

2-(N'-n-Hexylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide

{2-amino-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide and n-hexylamine} : yield 56.9% ; mp 168-169°C (EtOH); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)ppm : 0.86 (3H. t), 1.25-1.83 (15H. m), 2.79 (2H. d), 3.01 (2H. dd), 3.17 (2H. t), 4.26 (1H. s), 6.91 (1H. t), 7.13-7.40 (12H. m), 7.57 (1H. d), 8.21 (1H. d), 8.57 (1H. t), 9.95 (1H. s).

#### EXAMPLE 5

2-(N'-n-Heptylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide

{2-amino-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide and

n-heptylamine} : yield 67%; mp 146-148°C <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)ppm : 0.86 (3H, t), 3.00 (2H, dd), 3.15 (2H, m), 4.27 (1H, s), 6.89-7.58 (14H, m), 8.04 (1H, d), 8.19 (1H, q), 8.59 (1H, t), 9.93 (1H, s).

#### EXAMPLE 6

5    **2-(N'-n-Octylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide**  
          {2-amino-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide and  
n-octylamine} : yield 72.1%; mp 155-157°C (EtOH); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)ppm :  
0.86 (3H, t), 1.25-1.83 (19H, m), 2.79 (2H, d), 3.01 (2H, dd), 3.15 (2H, t), 4.26  
(1H, s), 6.91 (1H, t), 7.13-7.41 (12H, m), 7.57 (1H, d), 8.21 (1H, d), 8.58 (1H, t),  
10    9.95 (1H, s).

#### EXAMPLE 7

**2-(N'-n-Butylureido)-N-(1-diphenylmethylpiperidin-4-yl)benzamide**  
          {2-amino-N-(1-diphenylmethylpiperidin-4-yl)benzamide and n-butyl-  
amine} : yield 93.0%; mp 204-206°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.92 (3H, t), 1.23-  
15    1.67 (6H, m), 2.04 (4H, m), 2.84 (2H, m), 3.24 (2H, q), 4.11 (1H, m), 4.28 (1H, s),  
4.53 (1H, t), 6.55 (1H, d), 6.94 (1H, dd), 7.15-7.44 (12H, m), 8.40 (1H, d), 10.26  
(1H, s).

#### EXAMPLE 8

**2-(N'-n-Pentylureido)-N-(1-diphenylmethylpiperidin-4-yl)benzamide**  
20        {2-amino-N-(1-diphenylmethylpiperidin-4-yl)benzamide and n-  
pentylamine} : yield 65.0%; mp 199-201°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.89 (3H, t),  
1.29-1.70 (8H, m), 1.92-2.15 (4H, m), 2.79-2.88 (2H, m), 3.23 (2H, q), 3.87-4.05  
(1H, m), 4.28 (1H, s), 4.56 (1H, t), 6.08 (1H, d), 6.91-7.44 (13H, m), 8.41 (1H, d),  
10.25 (1H, s).

#### 25    EXAMPLE 9

**2-(N'-n-Hexylureido)-N-(1-diphenylmethylpiperidin-4-yl)benzamide**

          {2-amino-N-(1-diphenylmethylpiperidin-4-yl)benzamide and n-hexyl-  
amine} : yield 52.0%; mp 192-194°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.87 (3H, t), 1.25-  
1.67 (10H, m), 1.92-2.13 (4H, m), 2.79-2.87 (2H, m), 3.24 (2H, q), 3.88-4.02 (1H,

m). 4.28 (1H. s). 4.54 (1H. t). 6.05 (1H. d). 6.91-7.46 (13H. m). 8.41 (1H. d), 10.27 (1H. s).

#### EXAMPLE 10

##### 2-(N'-n-Octylureido)-N-(1-diphenylmethylpiperidin-4-yl)benzamide

5 {2-amino-N-(1-diphenylmethylpiperidin-4-yl)benzamide and n-octyl-amine} : yield 51.0%; mp 149-151°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.87 (3H. t), 1.23-1.68 (14H. m). 1.92-2.15 (4H. m), 2.80-2.88(2H. m), 3.23 (2H. q), 3.86-4.02 (1H, m). 4.28 (1H. s). 4.57 (1H. t). 6.06 (1H. d). 6.91-7.48 (13H. m). 8.41 (1H, d), 10.26 (1H. s).

#### 10 EXAMPLE 11

##### 2-(N'-n-Nonylureido)-N-(1-diphenylmethylpiperidin-4-yl)benzamide

{2-amino-N-(1-diphenylmethylpiperidin-4-yl)benzamide and n-nonyl-amine} : yield 94.0%; mp 149-150°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.87 (3H. t), 1.25 (12H. m). 1.56 (6H. m). 2.04 (4H. m). 2.84 (2H. m), 3.23 (2H. q), 3.91 (1H. m), 15 4.28 (1H. s). 4.54 (1H. t). 6.05 (1H. d), 6.94 (1H. dd), 7.15-7.44 (12H. m), 8.40 (1H. d). 10.26 (1H. s).

#### EXAMPLE 12

##### 2-(N'-n-Decylureido)-N-(1-diphenylmethylpiperidin-4-yl)benzamide

{2-amino-N-(1-diphenylmethylpiperidin-4-yl)benzamide and n-decyl-amine} : yield 83.0%; mp 204-206°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.92 (3H. t), 1.23-1.67 (6H. m). 2.04 (4H. m). 2.84 (2H.m), 3.24 (2H. q), 4.11 (1H. m), 4.28 (1H, s), 20 4.53 (1H. t). 6.55 (1H. d). 6.94 (1H. dd), 7.15-7.44 (12H. m), 8.40 (1H. d), 10.26 (1H. s).

#### EXAMPLE 13

##### 25 3,5-Dimethoxy-2-(N'-n-heptylureido)-N-(1-diphenylmethylpiperidin-4-yl)-benzamide

{2-amino-3,5-dimethoxy-N-(1-diphenylmethylpiperidin-4-yl)benzamide and n-heptylamine} : yield 64.0%; mp 195-198°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.85 (3H. t). 2.78 (2H. d), 3.18 (2H. dd), 3.76 (3H. s), 3.81 (3H, s), 3.95 (1H,m),

4.23 (1H, s), 4.86 (1H, t), 5.89 (1H, s), 6.48 (1H, d), 6.84 (1H, d), 7.35 (1H, d).

#### EXAMPLE 14

**5-Fluoro-2-(N'-n-heptylureido)-N-(1-diphenylmethylpiperidin-4-yl)benzamide**

5 {2-amino-5-fluoro-N-(1-diphenylmethylpiperidin-4-yl)benzamide and n-heptylamine} : yield 67% : mp 208-210°C: <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.87 (3H, t), 2.58 (2H, d), 3.22 (2H, dd), 3.90 (1H, m), 4.23 (1H, s), 4.52 (1H, t), 5.05 (1H, d), 8.34 (1H, q), 9.94 (1H, s).

#### EXAMPLE 15

10 **2-(N'-n-Heptylureido)-3-isopropyl-N-(1-diphenylmethylpiperidin-4-yl)benzamide**

{2-amino-3-isopropyl-N-(1-diphenylmethylpiperidin-4-yl)benzamide and n-heptylamine} : yield 71.2%; mp 209-212°C: <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)ppm : 0.84 (3H, t), 1.21 (6H, d), 3.02 (2H, q), 3.10 (1H, m), 3.69 (1H, m), 4.29 (1H, s), 15 6.50 (1H, t), 7.14-7.42 (13H, m), 7.66 (1H, s), 8.03 (1H, d).

#### EXAMPLE 16

**2-(N'-n-Heptylureido)-5-nitro-N-(1-diphenylmethylpiperidin-4-yl)benzamide**

{2-amino-5-nitro-N-(1-diphenylmethylpiperidin-4-yl)benzamide and n-heptylamine} : yield 52.0% : mp 165-166°C: <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.86 (3H, 20 t), 1.27-1.96 (12H, m), 2.02 (4H, m), 2.89 (2H, q), 3.24 (2H, q), 3.92 (1H, m), 4.30 (1H, s), 4.76 (1H, t), 6.33 (1H, d), 7.16-7.42 (10H, m), 8.25 (1H, dd), 8.30 (1H, d), 8.67 (1H, d), 10.86 (1H, s).

#### EXAMPLE 17

25 **2-(N'-n-Heptylureido)-N-[3-(1-diphenylmethylpyrrolidin-3-yl)propyl]benzamide**

{2-amino-N-[3-(1-diphenylmethylpyrrolidin-3-yl)propyl]benzamide and n-heptylamine} : yield 76.1%; mp 109-111°C: <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.88 (3H, t), 1.24-1.62 (15H, m), 1.92-2.08 (2H, m), 2.10-2.24 (1H, m), 2.31-2.43 (1H, m), 2.52-2.63 (1H, m), 2.71 (1H, dd), 3.24 (1H, dt), 3.37 (2H, dt), 4.16 (1H, s),

4.64 (1H, t), 6.22 (1H, t), 6.92 (1H, dd), 7.10-7.50 (12H, m), 8.41 (1H, d), 10.26 (1H, s).

#### EXAMPLE 18

##### 2-(N'-n-Heptylureido)-N-(2,6-diisopropylphenyl)benzamide

5 {2-amino-N-(2,6-diisopropylphenyl)benzamide and n-heptylamine} :  
yield 63.2%; mp 123-125°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.88 (3H, t), 1.16-1.30 (20H, m), 1.45-1.51 (2H, m), 3.07-3.25 (4H, m), 4.59-4.63 (1H, t), 7.04-7.10 (1H, m), 7.25-7.71 (6H, m), 8.52-8.55 (1H, d), 10.36 (1H, s).

#### EXAMPLE 19

##### 10 2-(N'-n-Heptylureido)-5-hydroxy-N-(3,3-diphenylpropyl)benzamide

{2-amino-5-hydroxy-N-(3,3-diphenylpropyl)benzamide and n-heptylamine} : yield 81.3%; mp 161.0-161.5°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.87 (3H, t), 1.26 (8H, t), 1.39-1.55 (2H, m), 2.32 (2H, dt), 3.17 (2H, dt), 3.30 (2H, dt), 3.96 (1H, t), 4.69 (1H, t), 6.46 (1H, t), 6.58 (1H, d), 6.71 (1H, dd), 7.04 (1H, s), 7.13-  
15 7.30 (10H, m), 7.75 (1H, d), 9.41 (1H, s).

#### EXAMPLE 20

##### 2-[N'-(3,5-Di-t-butyl-4-hydroxyphenyl)ureido]-N-(1-diphenylmethylpiperidin-4-yl)-benzamide

{2-amino-N-(1-diphenylmethylpiperidin-4-yl)benzamide and 4-amino-2,6-di-t-butylphenol [G. M. Coppinger, Tetrahedron 18, 61 (1962)]} : yield  
20 27.0%; mp 218-225°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 1.43 (18H, m), 1.55-1.64 (2H, m), 1.89-2.13 (2H, m), 3.90-3.98 (1H, m), 4.37 (1H, s), 5.07 (1H, s), 5.43 (1H, d), 6.33 (1H, s), 6.95 (1H, t), 7.16-7.46 (14H, m), 8.43 (1H, d), 10.35 (1H, s).

#### EXAMPLE 21

##### 25 2-[N'-(4-n-Heptylphenyl)ureido]-N-(1-diphenylmethylpiperidin-4-yl)-benzamide

{2-amino-N-(1-diphenylmethylpiperidin-4-yl)benzamide and 4-heptylaniline} : yield 86.0%; mp 173-175°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.87 (3H, t), 1.28 (6H, m), 1.58 (6H, m), 2.01 (4H, m), 2.25 (2H, t), 2.83 (2H, m), 3.88 (1H,



bs), 4.26 (1H, s), 6.07 (1H, d), 6.54 (1H, s), 6.90-7.43 (18H, m), 8.37 (1H, d), 10.41 (1H, s).

#### EXAMPLE 22

2-[N'-(2-t-Butoxycarbonylaminoethyl)ureido]-N-(1-diphenylmethylpiperidin-4-yl)-benzamide

{2-amino-N-(1-diphenylmethylpiperidin-4-yl)benzamide and t-butyl N-(2-aminoethyl) carbamate} : yield 89.0%; mp 226-228°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 1.41 (9H, s), 1.63 (2H, m), 1.94-2.12 (4H, m), 2.84 (2H, m), 3.33 (4H, m), 3.92 (1H, m), 4.28 (1H, s), 4.97 (2H, m), 6.10 (1H, d), 6.96 (1H, t), 7.25 (12H, m), 8.36 (1H, d), 10.29 (1H, s).

#### EXAMPLE 23

1-[2-(N'-n-Heptylureido)benzoyl]-4-(2-methoxyphenyl)piperazine

{1-(2-aminobenzoyl)-4-(2-methoxyphenyl)piperazine and n-heptylamine} : yield 64.0%; mp 209-212°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.88 (3H, t), 3.19 (2H, q), 3.87 (3H, s), 4.96 (1H, m), 3.69 (1H, m), 4.29 (1H, t), 6.87-7.39 (7H, m), 8.04 (1H, d), 8.09 (1H, d).

#### EXAMPLE 24

1-[2-(N'-n-Heptylureido)benzoyl]-4-diphenylmethylpiperazine

{1-(2-aminobenzoyl)-4-diphenylmethylpiperazine and n-heptylamine} : yield 86.0%; mp 125-127°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.89 (3H, t), 1.29-1.31 (8H, m), 1.47-1.49 (2H, m), 2.32-2.50 (4H, m), 3.19 (2H, q), 3.41-3.80 (4H, m), 4.23 (1H, s), 3.90 (1H, t), 6.93 (1H, t), 7.09-7.41 (12H, m), 8.01 (1H, s), 8.04 (1H, d).

#### EXAMPLE 25

2-[N'-(2-Aminoethyl)ureido]-N-(1-diphenylmethylpiperidin-4-yl)benzamide

{2-amino-N-(1-diphenylmethylpiperidin-4-yl)benzamide and 1,2-diaminoethane} : yield 90.0 % ; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 1.58-2.07 (6H, m), 2.83 (4H, m), 3.25 (2H, m), 3.87 (1H, s), 4.25 (1H, s), 5.70 (1H, s), 6.45 (1H, d), 6.92 (1H, t), 7.14-7.4 (12H, m), 8.30 (1H, d), 10.11 (1H, s).

**EXAMPLE 26**

**2-[N'-(2-Aminoethyl)ureido]-N-[(1-diphenylmethylpiperidin-4-yl)methyl]-benzamide**

{2-amino-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide and  
5 1,2-diaminoethane} : yield 97%; mp 101-103°C: <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 1.34-1.43 (2H. m), 1.54-1.68 (3H. m), 1.83 (2H. t), 2.81-2.92 (6H. m), 3.27-3.31 (4H, m), 4.24 (1H. s), 5.31 (1H. bt), 6.39 (1H. bt), 6.82 (1H. d), 7.10-7.42 (12H, m), 8.33 (1H. d, J=8.2Hz), 10.20 (1H. s).

**EXAMPLE 27**

10 **2-(N'-n-Heptylureido)-N-(1-phenoxy carbonylpiperidin-4-yl)benzamide**

Phenyl chloroformate (5.0ml, 40mmol) was added to a solution of 2-amino-N-(1-benzylpiperidin-4-yl)benzamide (3.1g, 10mmol) in chloroform (50ml). The mixture was refluxed for 2 hours. After cooling, ether was added and then the solution was washed with saturated NaHCO<sub>3</sub> solution and brine. The  
15 organic layer was concentrated to give 2-phenoxy carbonylamino-N-(1-phenoxy carbonylpiperidin-4-yl)benzamide.

A solution of 2-phenoxy carbonylamino-N-(1-phenoxy carbonylpiperidin-4-yl)benzamide (1.6g, 3.5mmol) and n-heptylamine (0.45g, 3.9mmol) in toluene (20ml) was refluxed for 4 hours and then concentrated. The residue was  
20 purified by column chromatography on silica gel (50% ethyl acetate in petroleum ether) to give 2-(N'-n-heptylureido)-N-(1-phenoxy carbonylpiperidin-4-yl)benzamide : yield 95.0%; mp 142-144°C: <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.88 (3H. t) 1.28-1.33 (7H. m), 1.9-1.62 (4H. m), 2.05-2.17 (2H. m), 3.04-3.19 (2H. m), 3.25 (2H. q), 4.10-4.15 (1H. m), 4.24-4.40 (2H. m), 4.59 (1H. t), 6.35 (1H. d), 6.92 (1H, t),  
25 6.97-7.44 (8H. m), 8.40 (1H. d), 10.20 (1H. s).

**EXAMPLE 28**

**2-(N'-n-Heptylureido)-N-[2-(1-diphenylmethylpiperidin-4-yl)ethyl]benzamide**

A solution of octanoic acid (0.5g, 3.5mmol), diphenylphosphoryl azide (1.0g, 3.6mmol) and Et<sub>3</sub>N (0.4g, 4mmol) in acetonitrile (10ml) was refluxed

for 1 hour and then concentrated. The residue was dissolved in chloroform (10ml). 2-Amino-N-[2-(1-diphenylmethylpiperidin-4-yl)ethyl]benzamide (0.74g, 1.79 mmol) was added to the solution. The mixture was refluxed for 50 hours and then concentrated. The residue was purified by column chromatography on silica gel (10 % to 30% ethyl acetate in hexane) to give 2-(N'-n-heptylureido)-N-[2-(1-diphenyl-methylpiperidin-4-yl)ethyl]benzamide (0.88 g, 88.9 %) : mp 125-127°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.88 (3H, t), 1.09-1.43 (10H, m), 1.44-1.77 (7H, m), 1.78-1.93 (2H, m), 2.88 (2H, d), 3.24 (2H, dt), 3.42 (2H, dt), 4.23 (1H, s), 4.58 (1H, t), 6.16 (1H, t), 6.93 (1H, t), 7.13-7.45 (12H, m), 8.41 (1H, d), 10.28 (1H, s).

In a similar manner, the following compounds (Examples 29 to 42) were prepared from other appropriately substituted 2-amino-benzamides and other appropriately substituted carboxylic acids which were described in braces : {} after titles of these compounds.

#### EXAMPLE 29

2-(N'-n-Pentylureido)-N-[2-(1-diphenylmethylpiperidin-4-yl)ethyl]benzamide {2-amino-N-[2-(1-diphenylmethylpiperidin-4-yl)ethyl]benzamide and n-hexanoic acid} : yield 40.6%: mp 124-127 C: <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.90 (3H, t), 1.25-1.44 (6H, m), 1.47-1.61 (5H, m), 1.61-1.71 (2H, m), 1.83 (2H, t), 2.88 (2H, d), 3.27 (2H, dt), 3.45 (2H, dt), 4.23 (1H, s), 4.60 (1H, t), 6.15 (1H, t), 6.56 (1H, t), 7.13-7.44 (12H, m), 8.41 (1H, d), 10.28 (1H, s).

#### EXAMPLE 30

2-(N'-n-Hexylureido)-N-[2-(1-diphenylmethylpiperidin-4-yl)ethyl]benzamide {2-amino-N-[2-(1-diphenylmethylpiperidin-4-yl)ethyl]benzamide and n-heptanoic acid} : yield 91.3%: mp 143-144°C: <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.88 (3H, t), 1.22-1.46 (8H, m), 1.46-1.75 (7H, m), 1.83 (2H, t), 2.88 (2H, d), 3.24 (2H, dt), 3.42 (2H, dt), 4.23 (1H, s), 4.58 (1H, t), 6.17 (1H, t), 6.93 (1H, t), 7.13-7.44 (12H, m), 8.40 (1H, d), 10.24 (1H, s).

#### EXAMPLE 31

2-(N'-n-Heptylureido)-5-dimethylamino-N-(1-diphenylmethylpiperidin-4-yl)-

**benzamide**

{2-amino-5-dimethylamino-N-(1-diphenylmethylpiperidin-4-yl)benzamide and n-octanoic acid} : yield 70.0%; mp 204-206°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.86 (3H, t), 2.86 (6H, m), 3.76 (1H, m), 4.30 (1H, s), 6.81-7.84 (3H, m), 7.15-7.44 (10H, m), 8.35 (1H, d), 9.08 (1H, s).

**EXAMPLE 32****2-(N'-n-Heptylureido)-3-dimethylamino-N-(1-diphenylmethylpiperidin-4-yl)-benzamide**

{2-amino-3-dimethylamino-N-(1-diphenylmethylpiperidin-4-yl)benzamide and n-octanoic acid} : yield 38.0%; mp 203°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.85 (3H, t), 1.12-1.34 (8H, m), 1.35-1.61 (4H, m), 1.92 (2H, d), 2.03 (2H, t), 2.55 (6H, s), 2.80 (2H, d), 3.16 (2H, dt), 3.86-4.05 (1H, m), 4.24 (1H, s), 5.56 (1H, d), 6.66 (1H, d), 6.93 (1H, s), 7.09-7.41 (13H, m).

**EXAMPLE 33****2-(N'-n-Heptylureido)-N-methyl-N-[(1-diphenylmethylpiperidin-4-yl)methyl]-benzamide**

{2-amino-N-methyl-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide and n-octanoic acid} : yield 68.0%; mp 140°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.88 (3H, t), 1.24-1.78 (19H, m), 2.93 (3H, s), 2.85-3.20 (5H, m), 3.42 (1H, d), 4.21 (1H, s), 5.07 (1H, t), 6.98-7.36 (14H, m), 7.98 (1H, s).

**EXAMPLE 34****2-(N'-n-Heptylureido)-N-(pyridin-3-yl)benzamide**

{2-amino-N-(pyridin-3-yl)benzamide and n-octanoic acid} : yield 85.2%; mp 144.5°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.85 (3H, t), 1.10-1.34 (8H, m), 1.35-1.49 (2H, m), 3.03 (2H, q), 7.05 (1H, t), 7.21 (1H, bt), 7.38-7.48 (2H, m), 7.72 (1H, d), 8.09-8.14 (1H, m), 8.22 (1H, d), 8.32-8.35 (1H, m), 8.90 (1H, t), 9.24 (1H, s), 10.57 (1H, s).

**EXAMPLE 35****2-(N'-n-Heptylureido)-N-(pyridin-2-yl)benzamide**

{2-amino-N-(pyridin-2-yl)benzamide and n-octanoic acid} : yield 84.0% : mp 118.5°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.88 (3H, t), 1.18-1.40 (8H, m), 1.44-1.62 (2H, m), 3.27 (2H, q), 4.66 (1H, t), 6.99-7.11 (2H, m), 7.49 (1H, t), 7.63 (1H, d), 7.76 (1H, t), 8.24 (1H, d), 8.29-8.33 (1H, m), 8.49 (1H, d), 8.68 (1H, s),  
 5 10.11 (1H, s).

**EXAMPLE 36**

**2-[N'-(1,1-Dimethyltridecyl)ureido]-N-(1-diphenylmethylpiperidin-4-yl)benzamide**

{2-amino-N-(1-diphenylmethylpiperidin-4-yl)benzamide and 2,2-dimethyl tetradecanoic acid} : yield 38.0%: mp 146-148°C: <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.88 (3H, t), 1.24-1.32 (22H, m), 1.55 (6H, s), 1.62-1.66 (2H, m), 1.96-2.12 (4H, m), 2.83-2.87 (2H, m), 3.87-3.94 (1H, m), 4.28 (1H, s), 4.44 (1H, t), 6.08 (1H, d), 6.89-6.95 (1H, t), 7.16-7.42 (12H, m), 8.37 (1H, d), 10.04 (1H, s).

**EXAMPLE 37**

15 **2-[N'-(2,6-Diisopropylphenyl)ureido]-N-(1-diphenylmethylpiperidin-4-yl)-benzamide**

{2-amino-N-(1-diphenylmethylpiperidin-4-yl)benzamide and 2,6-diisopropyl benzoic acid} : yield 63.0%: mp 118°C: <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 1.17 (12H, d), 1.43-1.49 (2H, m), 1.816 (2H, m), 1.96-2.04 (2H, m), 2.77-2.81 (2H, m), 3.23-3.33 (2H, m), 3.75 (1H, m), 4.25 (1H, s), 5.82-5.91 (2H, m), 6.95 (1H, t), 7.16-7.41 (15H, m), 8.43 (1H, d), 9.53-9.54 (1H, m).

**EXAMPLE 38**

**1-[2-(N'-n-Heptylureido)benzoyl]-4-diphenylmethylhomopiperazine**

{1-(2-aminobenzoyl)-4-diphenylmethylhomopiperazine and n-octanoic acid} : yield 82.0%: mp 125°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.88 (3H, t), 1.29 (8H, bs), 1.42-1.56 (2H, s), 1.65-1.78 (1H, m), 1.83-1.95 (4H, m), 2.51-2.82 (4H, m), 3.13-3.28 (1H, m), 3.35-3.61 (2H, m), 3.67-3.88 (2H, m), 4.56 (1H, d), 4.85-5.00 (1H, m), 6.98 (1H, dt), 7.09-7.49 (12H, m), 7.82-8.16 (2H, m).

**EXAMPLE 39**

**1-[2-(N'-n-Heptylureido)benzoyl]-4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)piperazine**

{1-(2-aminobenzoyl)-4-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)piperazine and n-octanoic acid} : yield 39.0%: mp 144°C: <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.89 (3H, t), 1.18-1.43 (8H, m), 1.44-1.63 (2H, m), 2.18-2.48 (4H, m), 2.77-2.88 (2H, m), 3.22 (2H, q), 3.26-3.93 (4H, m), 3.94-4.02 (3H, m), 4.67 (1H, t), 6.92 (1H, t), 7.04-7.35 (10H, m), 8.07 (2H, t).

**EXAMPLE 40**

**2-(N'-n-Heptylureido)-N-[3-(1-diphenylmethylpiperidin-4-yl)propyl]benzamide**

{2-amino-N-[3-(1-diphenylmethylpiperidin-4-yl)propyl]benzamide and n-octanoic acid} : yield 45.3%: mp 123-124.5°C (AcOEt/hexane); <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.88 (3H, t), 1.14-1.40 (13H, m), 1.45-1.66 (6H, m), 1.81 (2H, t), 2.87 (2H, d), 3.24 (1H, dt), 3.38 (2H, dt), 4.22 (1H, s), 4.60 (1H, t), 6.24 (1H, t), 6.93 (1H, t), 7.13-7.32 (7H, m), 7.34-7.44 (5H, m), 8.40 (1H, d), 10.28 (1H, s).

**EXAMPLE 41**

**N-(1-Benzylpiperidin-4-yl)-2-(N'-n-heptylureido)benzamide**

{2-amino-N-(1-benzylpiperidin-4-yl)benzamide and n-octanoic acid} : yield 48.4%: mp 134°C: <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.88 (3H, t), 1.20-1.40 (8H, m), 1.45-1.69 (4H, d), 2.18 (2H, t), 2.86 (2H, d), 3.24 (2H, q), 3.25 (2H, s), 3.83-4.03 (1H, m), 4.62 (1H, t), 6.13 (1H, d), 6.94 (1H, dt), 7.24-7.43 (7H, m), 8.40 (1H, dd), 10.26 (1H, s).

**EXAMPLE 42**

**N-(1-Benzylpiperidin-4-yl)-2-(N'-n-octylureido)benzamide**

{2-amino-N-(1-benzylpiperidin-4-yl)benzamide and n-nonanoic acid} : yield 81.9%: mp 129°C: <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.88 (3H, t), 1.17-1.41 (10H, m), 2.00 (2H, d), 2.18 (2H, t), 2.86 (2H, d), 3.25 (2H, q), 3.52 (2H, s), 3.83-4.02 (1H, m), 4.56 (1H, t), 6.06 (1H, d), 6.95 (1H, dt), 7.24-7.45 (7H, m), 8.42 (1H, dd), 10.29 (1H, s).

**EXAMPLE 43**

**N-[1-[2,6-Diisopropyl-4-(4-fluorophenyl)-5-(methoxymethyl)pyridin-3-yl]methylpiperidin-4-yl]-2-(N'-n-heptylureido)benzamide**

Step 1) : 10 % Pd/C was added to a solution of the N-(1-benzylpiperidin-4-yl)-2-(N'-n-heptylureido)benzamide (1.4g, 3.1mmol) obtained in Example 41 in methanol (25ml) under nitrogen. The mixture was shaken under 50 psi hydrogen pressure for 5 hours, and then filtered under nitrogen. The filtrate was concentrated. The residue was purified by column chromatography on silica gel (50 % methanol and 0.8% NH<sub>4</sub>OH in dichloromethane) to give N-(piperidin-4-yl)-2-(N'-n-heptylureido)benzamide : 48.4%: mp 159°C.

Step 2) : N-(Piperidin-4-yl)-2-(N'-n-heptylureido)benzamide (0.96g, 2.7mmol) and NaBH<sub>3</sub>CN (0.17g, 2.7mmol) were added into a solution of 2,6-diisopropyl-4-(4-fluorophenyl)-3-formyl-5-methoxymethylpyridine (0.9g, 2.7 mmol) in MeOH (30ml). The mixture was stirred at room temperature for 72 hours, and then water was added at 0°C, extracted with dichloromethane, dried (MgSO<sub>4</sub>) and concentrated. The residue was purified by column chromatography on silica gel (10 to 50 % ethyl acetate in hexane) to give N-[1-[2,6-diisopropyl-4-(4-fluorophenyl)-5-(methoxymethyl)pyridin-3-yl]methylpiperidin-4-yl]-2-(N'-n-heptylureido)benzamide (0.65 g, 35.7 %) : mp 123°C: <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.88 (3H, t), 1.17-1.46 (22H, m), 1.49-1.66 (2H, m), 1.80-2.00 (4H, m), 2.57 (2H, d), 3.09-3.53 (9H, m), 3.68-3.89 (1H, m), 3.49 (2H, s), 4.53 (1H, t), 5.98 (1H, d), 6.93 (1H, t), 7.05-7.24 (4H, m), 7.33-7.48 (2H, m), 8.41 (1H, d), 10.30 (1H, s).

The following compound (Example 44) was prepared in a similar manner, but replacing N-(1-benzylpiperidin-4-yl)-2-(N'-n-heptylureido)benzamide with N-(1-benzylpiperidin-4-yl)-2-(N'-n-octylureido)benzamide.

**EXAMPLE 44**

**N-[1-[2,6-Diisopropyl-4-(4-fluorophenyl)-5-(methoxymethyl)pyridin-3-yl]methylpiperidin-4-yl]-2-(N'-n-octylureido)benzamide**

Yield 34.1%; mp 132°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.88 (3H, t), 1.17-

1.46 (24H, m), 1.49-1.66 (2H, m), 1.80-2.00 (4H, m), 2.57 (2H, d), 3.09-3.55 (9H, m), 3.68-3.89 (1H, m), 3.49 (2H, s), 4.53 (1H, t), 5.98 (1H, d), 6.93 (1H, t), 7.05-7.24 (4H, m), 7.33-7.48 (2H, m), 8.41 (1H, d), 10.30 (1H, s).

#### EXAMPLE 45

##### 5 2-(N'-n-Heptylureido)-N-(1-diphenylmethylpiperidin-4-yl)benzamide

A mixture of 2-n-heptylamino-4H-3,1-benzoxazin-4-one (3.0g, 10mmol) and 4-amino-1-diphenylmethylpiperidine (3.0g, 10mmol) in toluene (20ml) was refluxed for 3 hours and then concentrated. The residue was purified by column chromatography on silica gel (20% ethyl acetate in hexane) to give 2-(N'-n-heptylureido)-N-(1-diphenylmethylpiperidin-4-yl)benzamide (2.3 g, 40 %) :  
10 mp 182°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.87 (3H, t), 1.27-1.30 (8H, m), 1.47-1.67 (4H, m), 1.95-2.12 (4H, m), 2.84 (2H, d), 3.24 (2H, q), 3.90-3.94 (1H, m), 4.26 (1H, s), 4.56 (1H, t), 6.09 (1H, d), 6.92-6.98 (1H, m), 7.16-7.44 (12H, m), 8.41 (1H, d), 10.26 (1H, s).

15 In a similar manner, the following compounds (Examples 46 to 53) were prepared from 2-n-heptylamino-4H-3,1-benzoxazin-4-one and other appropriately substituted amines which were described in braces : {} after titles of these compounds.

#### EXAMPLE 46

##### 20 N-(3,5-Di-t-butyl-4-hydroxyphenyl)-2-(N'-n-heptylureido)benzamide

{4-amino-2,6-t-butylphenol} : yield 22.0%; mp 211-214°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.86 (3H, d), 1.27-1.51 (28H, m), 3.16-3.23 (2H, q), 5.34 (1H, s), 5.60 (1H, s), 6.97 (1H, d), 7.00-7.45 (4H, m), 7.64 (1H, d), 8.34 (1H, d), 9.17 (1H, s), 9.84 (1H, s).

#### 25 EXAMPLE 47

##### N-(4-n-Heptylaniline)-2-(N'-n-heptylureido)benzamide

{4-n-heptylaniline} : yield 40.0%; mp 155-157°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.85-0.94 (6H, d), 1.28-1.32 (20H, m), 2.61 (2H, t), 3.25 (2H, q), 4.61 (1H, s), 6.94-7.03 (1H, m), 7.19-7.65 (6H, m), 8.00 (1H, s), 8.40 (1H, d),



10.01 (1H, s).

#### EXAMPLE 48

**N-(2-Bromo-6,11-dihydrodibenz[b,e]oxepin-11-yl)methyl-2-(N'-n-heptylureido)benzamide**

5 {11-aminomethyl-2-bromo-6,11-dihydrodibenz[b,e]oxepin} : yield 60.0% : mp 71-76°C: <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.88 (3H, t), 1.32-1.62 (8H, m), 3.23-3.30 (2H, m), 4.77 and 5.69 (2H, q), 6.39(1H, s), 6.90-7.43 (10H, m), 8.40 (1H, d), 10.21 (1H, d).

#### EXAMPLE 49

10 **N-[1-[2-(4,5-Diphenylimidazol-2-yl)thioethyl]piperidin-4-yl]-2-(N'-n-heptylureido)benzamide**

{2-[2-(4-aminopiperidin-1-yl)ethyl]thio-4,5-diphenylimidazole} : yield 45.6%: mp 160-161°C: <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.88 (3H, t), 1.08 (3H, ddd), 1.28-1.31 (8H, m), 1.51-1.56 (2H, m), 1.80(2H, d), 2.16 (2H, t), 2.93 (2H, t), 3.08-3.04 (4H, m), 3.24 (2H, dt), 3.80 (1H, m), 4.63 (1H, t), 5.27 (1H, d), 7.02-7.54 (13H, m), 8.43 (1H, d), 10.10 (1H, s).

#### EXAMPLE 50

**N-(3,3-Diphenylpropyl)-2-(N'-n-heptylureido)benzamide**

20 {3,3-diphenylpropylamine} : yield 60.0%: mp 118°C: <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.88 (3H,t), 1.06-1.72 (10H, b), 2.38 (2H,q), 3.00-3.60 (4H, m), 4.00 (1H, t), 4.60 (1H, t), 6.13 (1H, b), 6.64-7.52 (13H, m), 8.73 (1H, d), 10.28 (1H, s).

#### EXAMPLE 51

25 **N-[1-(2-Bromo-6,11-dihydrodibenz[b,e]oxepin-11-yl)piperidin-4-yl]-2-(N'-n-heptylureido)benzamide**

{11-(4-aminopiperidin-1-yl)-2-bromo-6,11-dihydrodibenz[b,e]oxepin} : yield 54.1%: mp 198-199°C: <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.82-0.93 (3H, m), 1.27-1.64 (12H, m), 1.93-1.95 (2H, m), 2.12 (2H, q), 2.70 (1H, d), 2.87 (1H, d), 3.24 (2H, q), 3.90-4.00 (2H, m), 4.57 (2H, t), 6.03 (1H, d), 6.77-6.96 (4H, m), 7.09-

7.45 (9H, m), 8.40 (1H, d), 10.26 (1H, s).

#### EXAMPLE 52

N-[2-(4,5-Diphenylimidazol-2-yl)thioethyl]-2-(N'-n-heptylureido)benzamide

{2-(2-aminoethylthio)-4,5-diphenylimidazole} : yield 35.9%; mp 285-288°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.97 (3H, t), 1.17-1.86 (10H, m), 3.24-3.31 (2H, m), 3.43 (2H, t), 3.86-3.92 (2H, m), 4.62-4.66 (1H, m), 6.36 (1H, t), 7.18-7.70 (13H, m), 8.36 (1H, d), 8.71-8.74 (1H, m), 10.53 (1H, s).

#### EXAMPLE 53

N-[2-(4,5-Diphenylimidazol-1-yl)ethyl]-2-(N'-n-heptylureido)benzamide

{1-(2-aminobenzoyl)-4-diphenylmethylpiperazine} : yield 86.0% ; mp 169.7°C : <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.89 (3H, t), 1.18-1.59 (10H, m), 3.20-3.7 (2H, dt), 3.45-3.51 (2H, dt), 4.06 (2H, t), 5.09-5.15 (1H, m), 6.45 (1H, t), 6.88-6.93 (1H, m), 7.15-7.46 (12H, m), 7.59 (1H, s), 8.45 (1H, d), 9.69-9.70 (1H, m).

#### EXAMPLE 54

2-(N'-n-Heptylureido)-N-(1-diphenylmethylpiperidin-3-yl)benzamide

Step 1) : A mixture of 2-(N'-n-heptylureido)-N-(pyridin-3-yl)benzamide obtained in the Example 34 (5.0g, 14mmol) and PtO<sub>2</sub> in acetic acid (70ml) was stirred at 40°C under hydrogen atmosphere (50 psi) for 17 hours and then filtered. The filtrate was neutralized with 30% NaOH solution, extracted with ethyl acetate and washed with saturated NaHCO<sub>3</sub> solution. The organic layer was dried (MgSO<sub>4</sub>) and concentrated. The residue was purified by column chromatography on silica gel (20% methanol and 0.8% NH<sub>4</sub>OH in dichloromethane) to give 2-(N'-n-heptylureido)-N-(piperidin-3-yl)benzamide (83.8%) : mp 165°C.

Step 2) : Bromodiphenylmethane (1.4g, 5.6mmol) was added to a solution of 2-(N'-n-heptylureido)-N-(piperidin-3-yl)benzamide (1.0g, 2.8mmol) and K<sub>2</sub>CO<sub>3</sub> (0.4g, 2.9mmol) in DMSO (5ml) at 0°C. The mixture was refluxed for 18 hours, poured into 1% NaHCO<sub>3</sub> solution, extracted with ethyl acetate and washed with 1% NaHCO<sub>3</sub> solution. The organic layer was dried (MgSO<sub>4</sub>) and

concentrated. The residue was purified by column chromatography on silica gel (25% to 50% ethyl acetate in hexane) to give 2-(N'-n-heptylureido)-N-(1-diphenylmethylpiperidin-3-yl)benzamide (0.3g, 20.5%) : mp 112°C. <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.88 (3H, t), 1.23-1.35 (8H, m), 1.47-1.85 (6H, m), 2.05-2.20 (1H, m), 2.35-2.49 (1H, m), 2.57-2.80 (2H, m), 3.24 (2H, q), 4.12-4.23 (1H, m), 4.35 (1H, s), 4.57-4.65 (1H, m), 6.90-7.55 (14H, m), 8.48 (1H, d), 10.37 (1H, s).

#### EXAMPLE 55

##### 2-(N'-n-Heptylureido)-5-amino-N-(1-diphenylmethylpiperidin-4-yl)benzamide

In a similar manner to that of the Example 54 step 1), but replacing 2-(N'-n-heptylureido)-N-(pyridin-3-yl)benzamide with 2-(N'-n-heptylureido)-5-nitro-N-(1-diphenylmethylpiperidin-4-yl)benzamide, 2-(N'-n-heptylureido)-5-amino-N-(1-diphenylmethylpiperidin-4-yl)benzamide was prepared. : yield 84.0%: mp 190-192°C: <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.84 (3H, t), 1.26 (8H, m), 1.53 (8H, m), 1.92-2.11 (4H, m), 2.82 (2H, m), 3.19 (2H, td), 3.55 (2H, m), 3.91 (1H, s), 4.27 (1H, s), 4.46 (1H, m), 6.08 (1H, d), 6.71 (1H, d), 6.78 (1H, dd), 7.15-7.41 (10H, m), 8.00 (1H, d), 9.27 (1H, s).

#### EXAMPLE 56

##### 2-(N'-n-Heptylureido)-5-methylsulfonylamino-N-(1-diphenylmethylpiperidin-4-yl)benzamide

Methanesulfonyl chloride (0.05ml, 0.65mmol) was added dropwise to a solution of triethylamine (0.09ml, 0.6mmol) and 2-(N'-n-heptylureido)-5-amino-N-(1-diphenylmethylpiperidin-4-yl)benzamide (0.32g, 0.59mmol) in dichloromethane (15ml) at 0°C. The mixture was stirred for 24 hours and then concentrated. The residue was purified by column chromatography on silica gel (50% ethyl acetate in cyclohexane) to give 2-(N'-n-heptylureido)-5-methylsulfonylamino-N-(1-diphenylmethylpiperidin-4-yl)benzamide (0.29g, 79.0%) : mp 180-182°C: <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.85 (3H, t), 1.28 (4H, m), 1.57 (6H, m), 2.00 (4H, m), 2.85 (2H, m), 2.95 (3H, s), 3.12 (2H, td), 3.90 (1H, m), 4.29 (1H, s),

4.63 (1H. m), 6.22 (1H. d), 6.46 (1H. d), 7.15-7.41 (12H. m), 8.36 (1H. d), 10.17 (1H. s).

#### EXAMPLE 57

##### 2-(N'-n-Heptylureido)-5-acetylamino-N-(1-diphenylmethylpiperidin-4-yl)benzamide

Triethylamine (0.098ml, 0.65mmol) and acetic anhydride (0.067ml, 0.07mmol) were added to a solution of the 2-(N'-n-heptylureido)-5-amino-N-(1-diphenylmethylpiperidin-4-yl)- benzamide (0.32g, 0.59mmol) in dichloromethane (3ml) at room temperature. The mixture was stirred for 24 hours and then concentrated. The residue was purified by column chromatography on silica gel (50% ethyl acetate in cyclohexane) to give 2-(N'-n-heptylureido)-5-acetylamino-N-(1-diphenylmethylpiperidin-4-yl)benzamide (0.33g, 96.0%) : mp 113-115°C, <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.86 (3H. t), 1.27 (8H. m), 1.49-1.69 (4H. m), 1.92-2.08 (4H. m), 2.17 (3H. s), 2.85 (2H. m), 3.22 (2H. q), 3.90 (1H. m), 4.28 (1H. s), 4.57 (1H. t), 6.40 (1H. d), 7.03 (1H. dd), 7.15-7.40 (11H. m), 8.06 (1H. d), 8.30 (1H, d), 10.10 (1H. s).

#### EXAMPLE 58

##### 2-(N'-n-Heptylureido)-5-(N'-n-butylureido)-N-(1-diphenylmethyl-piperidin-4-yl)benzamide

In a similar manner to that of Example 28, 2-(N'-n-heptylureido)-5-(N'-n-butylureido)-N-(1-diphenylmethylpiperidin-4-yl)benzamide was prepared from n-pentanoic acid and 2-(N'-n-heptylureido)-5-amino-N-(1-diphenylmethyl-piperidin-4-yl)benzamide : yield 79.0%: mp 209-211°C: <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) ppm : 0.83 (3H. t), 0.89 (3H. t), 3.77 (1H. m), 4.29 (1H. s), 6.08(1H. t), 7.00 (1H. bs), 7.15-7.40 (1H. m), 7.91 (1H. d), 8.30 (1H, s), 8.41 (1H. d), 9.06 (1H. d).

#### EXAMPLE 59

##### 2-[N'-(2-Di-n-butylaminoethyl)ureido]-N-(1-diphenylmethylpiperidin-4-yl)benzamide

To a solution of the 1,2-[N'-(2-aminoethyl)ureido]-N-(1-

diphenylmethylpiperidin-4-yl)- benzamide (0.33g, 0.7mmol) obtain in Example 25 and n-butyraldehyde (0.13ml, 1.44mmol) in methanol (5ml) was added by portions  $\text{NaBH}_3\text{CN}$  (0.32g, 5.1mmol) under stirring and the pH was adjusted at 6 by adding acetic acid. Then the reaction mixture was stirred at room temperature for 2 hours. A few drops of concentrated HCl were added in order to decompose the excess of reducing reagent. The mixture was concentrated. The residue was dissolved in dichloromethane, then basified to pH 10 with 10 % NaOH solution and extracted with dichloromethane. The organic layer was dried ( $\text{MgSO}_4$ ) and concentrated. The residue was purified by column chromatography on silica gel (ethyl acetate) to give 2-[N'-(2-di-n-butylaminoethyl)ureido]-N-(1-diphenylmethylpiperidin-4-yl)benzamide (0.15 g, 35.0 %) : mp 159-161°C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )ppm : 0.89 (6H, t), 2.10 (4H, m), 2.48 (4H, t), 2.64 (2H, m), 3.84 (2H, m), 3.31 (2H, q), 3.95 (1H, m), 4.28 (1H, s), 5.30 (1H, bs), 6.06 (1H, d), 6.96 (1H, t), 7.15-7.44 (12H, m), 8.34 (1H, d), 10.20 (1H, s).

#### EXAMPLE 60

##### 2-[N'-(2-n-Butylaminoethyl)ureido]-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide

To a solution of 2-[N'-(2-aminoethyl)ureido]-N-[(1-diphenylmethylpiperidin-4-yl)-methyl] benzamide (500mg, 1.0mmol), obtained as described in Example 26, and n-butyraldehyde (88 $\mu\text{l}$ , 1.1mmol), was added acetic acid (59 $\mu\text{l}$ ) and a few minutes later sodiumborohydride triacetate (305mg, 1.4mmol) at room temperature. After 12 hours, the excess sodiumborohydride triacetate was destroyed by 10%  $\text{NaHCO}_3$  solution (10ml) and the mixture was extracted with ethyl acetate. The organic layer dried ( $\text{MgSO}_4$ ) and concentrated. The residue was purified by flash column chromatography on silica gel (AcOEt 90/ MeOH 10/  $\text{NH}_4\text{OH}$  1) to give 2-[N'-(2-n-butylaminoethyl)ureido]-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide (110mg, 20%) : mp 148-150°C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )ppm : 0.91 (3H, t), 1.28-1.61 (9H, m), 1.7 (2H, t), 2.35 (1H, bs), 2.61 (2H, t), 2.78 (2H, t), 2.88-2.92 (2H, m), 3.27-3.38 (4H, m), 4.24 (1H, s), 5.37 (1H, bt),

6.39 (1H, bt), 6.92 (1H, t), 7.13-7.40 (12H, m), 8.35 (1H, d), 10.19 (1H, s).

The following compound (Example 61) was prepared in a similar manner, but replacing n-butyraldehyde with acetone.

#### EXAMPLE 61

5 2-[N'-(2-Isopropylaminoethyl)ureido]-N-[(1-diphenylmethylpiperidin-4-yl)-methyl]-benzamide

Yield 59.0%; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 1.06 (6H, d), 1.35-1.88 (8H, m), 2.75-2.93 (2H, 1H, 2H, m, h, t), 2.93-3.37 (4H, m), 4.24 (1H, s), 5.20 (1H, bt), 6.31 (1H, bt), 6.94 (1H, t), 7.14-7.43 (12H, m), 8.37 (1H, d), 10.23 (1H, s).

#### 10 EXAMPLE 62

2-(N'-n-Butylureido)-5-diethylamino-N-[(1-diphenylmethylpiperidin-4-yl)-methyl]-benzamide

Step 1) : To a solution of 5-fluoro-2-nitro-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide (prepared according to Preparation 24) (2.1g, 4.68mmol) in DMF (30ml) was added diethylamine (1.46ml, 14.06mmol). The solution was refluxed overnight and evaporated under reduced pressure to give 5-diethylamino-2-nitro-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide (2.28g, 97.5%) : mp 167-168°C.

Step 2) : To a solution of 5-diethylamino-2-nitro-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide (1.0g, 1.99mmol) was added PtO<sub>2</sub> (30mg). The solution was stirred under H<sub>2</sub> atmosphere (3 kg/cm<sup>2</sup>) for 3 hours. The catalysts were filtered off and the filtrate was evaporated to give 2-amino-5-diethylamino-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide, 930mg(100%) : mp 161-163°C.

Step 3) : To a solution of 2-amino-5-diethylamino-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide (593mg, 1.259mmol) in CHCl<sub>3</sub> (20ml) was added n-butylisocyanate (374mg, 3.779mmol). The solution was refluxed overnight and evaporated. The residue was purified by column chromatography on silica gel to give 5-diethylamino-2-(N'-n-butylureido)-N-[(1-diphenylmethyl-

piperidin-4-yl)methyl]benzamide. 366mg (51%) : mp 158-160°C;

<sup>1</sup>H NMR (CDCl<sub>3</sub>) ppm : 0.90 (3H, t), 1.12 (6H, t), 1.35-1.64 (9H, m), 1.84 (2H, t), 2.90 (2H, d), 3.19-3.31 (8H, m), 4.24 (1H, s), 4.47 (1H, bt), 6.38 (1H, bt), 6.75-6.82 (2H, m), 7.16-7.40 (10H, m), 7.87 (1H, d), 8.66 (1H, s).

5 In a similar manner to that of Example 62, but in Step 1) replacing diethylamine with other amines (dimethylamine, di-n-propylamine, di-n-butylamine, pyrrolidine, piperidine, morpholine, imidazole, pyrazole), metal alkoxides (sodium methoxide, sodium ethoxide, sodium cyclo-propylmethoxide), metal thioalkoxides (sodium thiomethoxide, sodium thioethoxide), in Step 2) using PtO<sub>2</sub>, Raney-Ni as a catalyst or Fe powder / HCl and in Step 3) using n-butylisocyanate or n-propylisocyanate, the compounds described in Examples 63 to 78 were prepared.

#### EXAMPLE 63

2-(N'-n-Butylureido)-5-dimethylamino-N-[(1-diphenylmethylpiperidin-4-yl)-methyl]-benzamide

15 {dimethylamine, n-butylisocyanate} : mp 201-203°C ; <sup>1</sup>H NMR (CDCl<sub>3</sub>) ppm : 0.90 (3H, t), 1.29-1.84 (12H, m), 2.89 (6H, s), 3.18 (2H, q), 3.28 (2H, t), 4.24 (1H, s), 4.62 (1H, bt), 6.46 (1H, bt), 6.73-6.82 (2H, m), 7.14-7.41 (11H, m), 7.86 (1H, d), 8.82 (1H, s).

#### 20 EXAMPLE 64

2-(N'-n-Butylureido)-5-(imidazol-1-yl)-N-[(1-diphenylmethylpiperidin-4-yl)-methyl]-benzamide

{imidazole, n-butylisocyanate} : mp 197-199°C ; <sup>1</sup>H NMR (CDCl<sub>3</sub>) ppm : 0.92 (3H, t), 1.33-1.87 (11H, m), 2.84 (2H, m), 3.17-3.28 (4H, m), 4.23 (1H, s), 6.18 (1H, bs), 7.12-7.40 (13H, m), 7.73 (1H, d), 7.93 (1H, s), 8.32 (1H, bt), 8.50 (1H, d), 10.33 (1H, s).

#### EXAMPLE 65

2-(N'-n-Butylureido)-5-(pyrrolidin-1-yl)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]-benzamide

{ pyrrolidine . n-butylicyanate } : mp 200-202°C ; <sup>1</sup> H NMR (CDCl<sub>3</sub>)ppm : 0.90 (3H. t), 1.21-1.88 (9H. m), 1.99 4H. m), 2.90 (2H. m), 3.15-3.32 (8H. m), 4.24 (1H. s), 4.88 (1H. bt), 6.47 (1H. bt), 6.55 (1H. d), 6.64 (1H, dd), 7.13-7.40 (10H. m), 7.85(1H. d), 8.63 (1H. bs).

5 **EXAMPLE 66**

**5-Dimethylamino-2-(N'-n-propylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]-benzamide**

{ dimethylamine . n-propylisocyanate } : mp 199-201°C ; <sup>1</sup> H NMR (CDCl<sub>3</sub>) ppm : 0.91 (3H. t), 1.25-1.90 (9H. m), 2.9 (8H. s+m), 3.17 (2H. q), 3.31 (2H. t), 4.25 (1H. s), 4.51 (1H. bt), 6.35 (1H.bt), 6.74 (1H. d), 6.85 (1H. dd), 7.14-7.41 (10H. m), 7.97 (1H. d), 8.93 (1H. bs).

**EXAMPLE 67**

**2-(N'-Butylureido)-5-methoxy-N-[(1-diphenylmethylpiperidin-4-yl)methyl]-benzamide**

15 { sodium methoxide . n-butylicyanate } : mp 206-208°C ; <sup>1</sup> H NMR (CDCl<sub>3</sub>) ppm : 0.92(3H. t), 1.34-1.89(11H. m), 2.91 (2H. m), 3.23 (2H. q), 3.33(2H. t), 3.78(3H. s), 4.24 (1H. s), 4.49 (1H. bt), 6.22 (1H, bt), 6.89 (1H, d), 6.99 (1H. dd), 7.14-7.40 (10H. m), 8.22 (1H. d), 9.61 (1H. s).

**EXAMPLE 68**

20 **2-(N'-n-Butylureido)-5-ethoxy-N-[(1-diphenylmethylpiperidin-4-yl)methyl]-benzamide**

{ sodium ethoxide , n-butylicyanate } : mp 191-193°C ; <sup>1</sup> H NMR (CDCl<sub>3</sub>)ppm : 0.85 (3H. t), 1.19-1.81 (14H. m), 2.83 (2H, d), 3.12-3.25 (4H, m), 3.92 (2H. q), 4.17 (1H. s), 4.45 (1H. t), 6.21 (1H. t), 6.82 (1H, d), 6.90 (1H, dd), 25 7.07-7.34 (10H. m), 8.12 (1H, d), 9.54 (1H, s).

**EXAMPLE 69**

**2-(N'-n-Butylureido)-5-cyclopropylmethoxy-N-[(1-diphenylmethylpiperidin-4-yl)methyl]-benzamide**

{ sodium cyclopropylmethoxide . n-butylicyanate } : mp 190-192°C



: <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.33 (2H. m), 0.62 (2H. m), 0.91 (3H. t), 1.23-1.69(9H, m), 1.83 (3H. m), 2.90 (2H. m), 3.17-3.30 (4H. m), 3.75 (2H. m), 4.24(1H, s), 4.60(1H. bt), 6.35 (1H. bt), 6.96 (2H. m), 7.13-7.41 (10H. m), 8.16 (1H, d), 9.55 (1H, s).

5 **EXAMPLE 70**

**2-(N'-n-Butylureido)-5-(morpholin-4-yl)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]-benzamide**

{ morpholine , n-butylisocyanate } : mp 208-210°C ; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.91 (3H. t), 1.31-1.88 (11H. m), 2.90 (2H. m), 3.06 (4H, m), 3.19 (2H. m), 3.30 (2H. m), 3.84 (4H. m), 4.25 (1H.s), 4.58 (1H. bt), 6.36 (1H. bt), 6.88(1H. d), 7.00(1H, dd), 7.14-7.40(10H. m), 8.13(1H. d), 9.41(1H. s).

**EXAMPLE 71**

**5-(Morpholin-4-yl)-2-(N'-n-propylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]-benzamide**

15 { morpholine , n-propylisocyanate } : mp 215-217°C ; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.92(3H. t), 1.34-1.88(9H. m), 2.90 (2H. m), 3.06(4H. m), 3.18(2H, m), 3.30(2H. m), 3.84(4H. m), 4.24(1H, s), 4.59 (1H. bt), 6.34 (1H. bt), 6.88 (1H, d), 7.01 (1H. dd), 7.14-7.40 (10H. m), 8.13 (1H. d), 9.42 (1H. s).

**EXAMPLE 72**

20 **5-Methylthio-2-(N'-n-propylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide**

{ sodium thiomethoxide , n-propylisocyanate } : mp 196-198°C ; <sup>1</sup>H NMR (CDCl<sub>3</sub>) ppm : 0.94 (3H, t), 1.36-1.70 (7H, m), 1.89 (2H, t), 2.45 (3H, s), 2.72 (2H. d), 3.20 (2H, q), 3.30 (2H, t), 4.25 (1H. s), 4.63 (1H. bt), 6.31 (1H, bt), 7.17-7.41 (12H. m), 8.34 (1H, d), 10.07 (1H, s).

**EXAMPLE 73**

**2-(N'-n-Butylureido)-5-methylthio-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide**

{ sodium thiomethoxide , n-butylisocyanate } : mp 206-208°C ; <sup>1</sup>H

NMR (CDCl<sub>3</sub>)ppm : 0.92 (3H. t), 1.30-1.89 (11H. m), 2.44 (3H. s), 2.91 (2H. m), 3.20-3.32 (4H. m), 4.25 (1H.s), 4.62 (1H. bt), 6.32 (1H. bt), 7.14-7.40 (12H. m), 7.91 (1H. d), 8.33 (1H. d), 10.05 (1H. s).

**EXAMPLE 74**

5 **2-(N'-n-Butylureido)-5-ethylthio-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide**

{ sodium thioethoxide . n-butyliisocyanate } : mp 159-160°C ; <sup>1</sup> H

NMR (CDCl<sub>3</sub>)ppm : 0.92 (3H. t), 1.24 (3H. t), 1.30-1.76 (14H. m), 1.85 (2H. t), 2.81-2.94 (4H. m), 3.21-3.33 (4H. m), 4.25 (1H. s), 4.61 (1H. bt), 6.28 (1H. bt),  
10 7.14-7.45 (12H. m), 8.37 (1H. d), 10.19 (1H. s).

**EXAMPLE 75**

**2-(N'-n-Butylureido)-5-(di-n-propyl)amino-N-[(1-diphenylmethylpiperidin-4-yl)methyl]-benzamide**

{ di-n-propylamine . n-butyliisocyanate } : mp 171.5-172.5°C ; <sup>1</sup> H

15 NMR(CDCl<sub>3</sub>)ppm : 0.90 (9H. t), 1.28-1.65 (11H. m), 1.83 (2H. t), 2.90 (2H. d), 3.16-3.32 (8H. m), 4.24 (1H. s), 4.55 (1H. bt), 6.47 (1H. bt), 6.70-6.75 (2H. m), 7.13-7.40 (12H. m), 7.76 (1H. d), 8.48 (1H. s).

**EXAMPLE 76**

**5-(di-n-Butyl)amino-2-(N'-n-butylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]-benzamide**

{ di-n-butylamine . n-butyliisocyanate } : mp 181.5-182.5°C ; <sup>1</sup> H

NMR (CDCl<sub>3</sub>)ppm : 0.86-0.94 (9H. m), 1.27-1.87 (17H. m), 2.89 (2H. d), 3.13-3.30 (8H. m), 4.23 (1H. s), 4.64 (1H. bt), 6.54 (1H. bt), 6.67-6.72 (2H. m), 7.13-7.40 (12H. m), 7.73 (1H. d), 8.49 (1H. s).

25 **EXAMPLE 77**

**(a) 2-(N'-n-Butylureido)-5-hydroxy-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide**

**and (b) 5-n-butylcarbamyloxy-2-(N'-n-butylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide**

{2-amino-5-hydroxy-N-[(1-diphenylmethyl)piperidin-4-yl)methyl]-benzamide and n-butylisocyanate} : mp 197-199°C ; <sup>1</sup>H NMR(CDCl<sub>3</sub>)ppm : 0.90 (3H, t), 1.20-1.90 (11H, m), 2.88 (2H, m), 3.18 (2H, td), 3.25 (2H, dd), 4.23 (1H, s), 5.31 (1H, bs), 6.88 (1H, dd), 6.97 (1H, d), 7.10-7.41 (11H, m), 7.95 (1H, d), 8.66 (1H, s), 9.40 (1H, s); and.

mp 153-155°C ; <sup>1</sup>H NMR(CDCl<sub>3</sub>)ppm : 0.90 (6H, t), 1.30-1.85 (15H, m), 2.86 (2H, m), 3.21 (6H, m), 4.21 (1H, s), 4.63 (1H, bs), 5.02 (1H, bs), 6.54 (1H, bs), 7.00-7.40 (12H, m), 8.34 (1H, d), 10.01(1H, s), respectively.

#### EXAMPLE 78

2-(N'-n-Butylureido)-4-chloro-N-[(1-diphenylmethyl)piperidin-4-yl)methyl]-benzamide

{2-amino-4-chloro-N-[(1-diphenylmethyl)piperidin-4-yl)methyl]benzamide and n-butylisocyanate} : mp 195-197°C ; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.93 (3H, t), 1.30-1.90 (11H, m), 2.91 (2H, m), 3.24 (2H, td), 3.31 (2H, dd), 4.25 (1H, s), 4.67 (1H, bs), 6.36 (1H, bs), 6.87 (1H, dd), 7.14-7.41 (11H, m), 8.51 (1H, d), 10.38 (1H, s).

In a similar manner to that of Example 62, but replacing Step 3) with the method of Example 1, the following compounds of Examples 79 to 105 were prepared.

#### 20 EXAMPLE 79

2-(N'-n-Heptylureido)-5-(imidazol-1-yl)-N-[(1-diphenylmethyl)piperidin-4-yl)methyl]-benzamide

{2-amino-5-(imidazol-1-yl)-N-[(1-diphenylmethyl)piperidin-4-yl)methyl]benzamide and n-heptylamine} : mp 183-185°C ; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.88 (3H, t), 1.24-1.86 (17H, m), 2.89 (2H, m), 3.21 (2H, q), 3.34 (2H, m), 4.22 (1H, s), 4.97 (1H, t), 7.00 (1H, s), 7.07-7.40 (13H, m), 7.55 (1H, d), 8.48 (1H, d), 8.74 (1H, t), 10.55 (1H, s).

#### EXAMPLE 80

2-(N'-n-Decylureido)-5-dimethylamino-N-[(1-diphenylmethyl)piperidin-4-

yl)methyl]-benzamide

{2-amino-5-dimethylamino-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide and n-decylamine} : mp 145-147°C ; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.88 (3H, t), 1.26-1.86 (27H, m), 2.87 (6H, s), 3.14 (2H, q), 3.26 (2H, t), 4.23 (1H, s), 4.76 (1H, bt), 6.73-6.78 (2H, m), 7.13-7.40 (11H, m), 7.77 (1H, d), 8.72 (1H, s).

EXAMPLE 81

2-(N'-n-Heptylureido)-5-methoxy-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide

{ 2-amino-5-methoxy-N-[(1-diphenylmethylpiperidin-4-yl)methyl]-benzamide and n-heptylamine} : mp 189-191°C ; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.88 (3H, t), 1.29-1.88 (17H, m), 2.90 (2H, m), 3.23 (2H, q), 3.30 (2H, t), 3.78 (3H, s), 4.25 (1H, s), 4.52 (1H, bt), 6.27 (1H, bt), 6.90 (1H, d), 6.98 (1H, dd), 7.14-7.40 (10H, m), 9.21 (1H, d), 9.61 (1H, s).

EXAMPLE 82

2-(N'-n-Heptylureido)-5-(morpholin-4-yl)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]-benzamide

{2-amino-5-(morpholin-4-yl)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide and n-heptylamine} : mp 153-155°C ; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.88 (3H, t), 1.28-1.88 (17H, m), 2.91 (2H, m), 3.06 (4H, t), 3.20 (2H, q), 3.30 (2H, t), 3.84 (4H, t), 4.24 (1H, s), 4.56 (1H, bt), 6.35 (1H, bt), 6.89 (1H, d), 7.01 (1H, dd), 7.14-7.40 (10H, m), 8.15 (1H, d), 9.45 (1H, s).

EXAMPLE 83

2-(N'-n-Heptylureido)-5-(piperidin-1-yl)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide

{2-amino-5-(piperidin-1-yl)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide and n-heptylamine} : mp 166-168°C ; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.88 (3H, t), 1.28-1.89 (23H, m), 2.90 (2H, m), 3.04 (2H, q), 3.23(2H, q), 3.30(2H, t), 4.24(1H, s), 4.48(1H, bt), 6.25 (1H, bt), 6.93 (1H, d), 7.05 (1H, dd),

7.14-7.40(10H, m), 8.12(1H, d), 9.51(1H, s).

#### EXAMPLE 84

**2-(N'-n-Heptylureido)-5-(pyrazol-1-yl)-N-[(1-diphenylmethylpiperidin-4-yl)-methyl]-benzamide**

5 {2-amino-5-(pyrazol-1-yl)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide and n-heptylamine} : mp 176-178°C ; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.88 (3H, t), 1.28-1.87 (17H, m), 2.96 (2H, m), 3.24(2H, q), 3.34 (2H, t), 4.26 (1H, s), 4.70 (1H, bs), 6.46 (1H, dd), 6.66 (1H, bs), 7.14-7.42 (10H, m), 7.56(1H, dd), 7.69(1H, d), 7.88(2H, m), 8.53(1H, d), 10.28(1H, s).

#### 10 EXAMPLE 85

**2-(N'-n-Heptylureido)-5-(pyrrolidin-1-yl)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]-benzamide**

{2-amino-5-(pyrrolidin-1-yl)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide and n-heptylamine} : mp 182-184°C ; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm :  
15 0.88 (3H, t), 1.27-1.98 (21H, m), 2.90 (2H, m), 3.13-3.29 (8H, m), 4.23 (1H, s), 4.55 (1H, bt), 6.55-6.63 (3H, m), 7.13-7.40 (10H, m), 7.80 (1H, d), 8.57(1H, bs).

#### EXAMPLE 86

**5-Ethoxy-2-(N'-n-heptylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]-benzamide**

20 {2-amino-5-ethoxy-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide and n-heptylamine} : mp 188-189°C ; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.88 (3H, t), 1.28-1.88 (20H, m), 2.90 (2H, d), 3.20 (2H, q), 3.29 (2H, t), 3.99 (2H, q), 4.24 (1H, s), 4.51 (1H, t), 6.29 (1H, t), 6.89(1H, d), 6.97 (1H, dd), 7.14-7.41 (10H, m), 8.19 (1H, d), 9.62 (1H, s).

#### 25 EXAMPLE 87

**5-Diethylamino-2-(N'-n-heptylureido)-N-[(1-diphenylmethylpiperidin-4-yl)-methyl]-benzamide**

{2-amino-5-diethylamino-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide and n-heptylamine} mp 149-151°C ; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.86

(3H, t), 1.00-1.80 (23H, m), 2.83 (2H, m), 3.17 (8H, m), 4.17 (1H, s), 4.40 (1H, bs), 6.30 (1H, bs), 6.72 (2H, m), 7.10-7.40 (10H, m), 7.81 (1H, d), 8.60 (1H, bs).

**EXAMPLE 88**

2-(N'-Ethylureido)-5-dimethylamino-N-[(1-diphenylmethylpiperidin-4-yl)-methyl]benzamide

{2-amino-5-dimethylamino-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide and ethylamine} : mp 186-188°C ; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 1.01 (3H, t), 1.20-1.90 (7H, m), 2.80 (2H, m), 2.87 (6H, s), 3.03 (2H, m), 3.17 (2H, bs), 4.30 (1H, s), 6.84 (3H, m), 7.18-7.44 (10H, m), 7.90 (1H, d), 8.53 (1H, bs), 9.24 (1H, s).

**EXAMPLE 89**

2-(N'-n-Heptylureido)-5-dimethylamino-N-[(1-diphenylmethylpiperidin-3-yl)methyl]-benzamide

{2-amino-5-dimethylamino-N-[(1-diphenylmethylpiperidin-3-yl)methyl]benzamide and n-heptylamine} : mp 142-144°C ; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.88 (3H, t), 1.12-2.12 (17H, m), 2.53-2.69 (2H, m), 2.86 (6H, s), 3.19 (2H, q), 3.32 (2H, t), 4.24 (1H, s), 4.60 (1H, t), 6.62-6.63 (2H, m), 6.81 (1H, d d), 7.11-7.37 (10H, m), 7.92 (1H, d), 8.84 (1H, s).

**EXAMPLE 90**

2-(N'-n-Heptylureido)-5-hydroxy-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide

{2-amino-5-hydroxy-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide and n-heptylamine} : mp 165-167°C ; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.86 (3H, t), 1.20-1.90 (17H, m), 2.88 (2H, m), 3.15 (2H, td), 3.23 (2H, dd), 4.23 (1H, s), 5.20 (1H, bt), 6.80 (1H, bt), 6.91 (2H, m), 7.10-7.40 (10H, m), 7.95 (1H, d), 8.62 (1H, s), 9.42 (1H, s).

**EXAMPLE 91**

5-(N-Acetyl-N-methyl)amino-2-(N'-n-heptylureido)-N-[(1-diphenylmethylpiperidin-4-yl)-methyl]benzamide

- {2-amino-5-(N-acetyl-N-methyl)amino-N-[(1-diphenylmethyl)piperidin-4-yl)methyl]benzamide and n-heptylamine} : mp 192-193°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.89 (3H, t), 1.29-1.90 (20H, m), 1.83 (3H, s), 2.92 (2H, d), 3.20 (3H, s), 3.20-3.29 (2H, m), 3.33 (2H, t), 4.26 (1H, s), 4.65 (1H, t), 6.77 (1H, bs),  
 5 7.14-7.40 (11H, m), 8.50 (1H, d), 10.49 (1H, bs).

**EXAMPLE 92**

**2-(N'-n-Heptylureido)-5-dimethylamino-N-[[1-bis(4-chlorophenyl)methyl]piperidin-4-yl]-methyl]benzamide**

- {2-amino-5-dimethylamino-N-[[1-bis(4-chlorophenyl)methyl]piperidin-4-yl] methyl]benzamide and n-heptylamine} : mp 216 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.88 (3H, t), 1.20-1.90 (17H, m), 2.80-3.05 (2H, m), 2.90 (6H, s), 3.19 (2H, d), 3.30 (2H, t), 4.21 (1H, s), 4.53 (1H, bt), 6.53 (1H, bt), 6.65-6.92 (2H, m), 7.17-7.47 (8H, m), 7.76-8.00 (1H, m), 8.88 (1H, s)

**EXAMPLE 93**

- 15 **2-(N'-n-Heptylureido)-5-dimethylamino-N-[[1-bis(4-fluorophenyl)methyl]piperidin-4-yl]-methyl]benzamide**

- {2-amino-5-dimethylamino-N-[[1-bis(4-fluorophenyl)methyl]piperidin-4-yl]methyl]benzamide and n-heptylamine} : mp 220 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.88(3H, t), 1.15-1.90 (17H, m), 2.78-3.02 (2H, m), 2.90 (6H, s),  
 20 3.19 (2H, q), 3.30 (2H, t), 4.23 (1H, s), 4.52 (1H, bt), 6.48 (1H, bt), 6.74 (1H, m), 6.84 (1H, d), 6.93-6.99 (4H, m), 7.29-7.34 (4H, m), 7.92 (1H, d), 8.88 (1H, s)

**EXAMPLE 94**

**2-(N'-n-Heptylureido)-5-dimethylamino-N-[[1-bis(4-methoxyphenyl)methyl]piperidin-4-yl]methyl]benzamide**

- 25 {2-amino-5-dimethylamino-N-[[1-bis(4-methoxyphenyl)methyl]piperidin-4-yl]methyl]benzamide and n-heptylamine} : mp 163 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.88 (3H, t), 1.12-1.96 (17H, m), 2.77-3.01 (2H, m), 2.90 (6H, s), 3.19 (2H, q), 3.29 (2H, t), 3.76 (6H, s), 4.17 (1H, s), 4.48 (1H, s), 6.40 (1H, s), 6.62-6.95 (6H, m), 7.17-7.40 (4H, m), 7.96 (1H, d), 8.95 (1H, s)

## EXAMPLE 95

2-(N'-n-Heptylureido)-5-dimethylamino-N-[1-(4-biphenylmethylpiperidin-4-yl)methyl]-benzamide

{2-amino-5-dimethylamino-N-[1-(4-biphenylmethylpiperidin-4-yl)-methyl]benzamide and n-heptylamine } : mp 186 °C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)ppm : 0.86 (3H, t), 1.27 (8H, m), 1.40 (2H, t), 1.58-1.63 (1H, m), 1.68 (2H, d), 2.02 (2H, t), 2.85 (6H, s), 3.02 (2H, q), 3.17 (2H, t), 3.50 (2H, s), 6.34 (1H, bt), 6.77 (1H, dd), 6.86 (1H, d), 7.28-7.45 (5H, m), 7.54-7.62 (4H, m), 7.79 (1H, d), 8.04 (1H, bt), 8.86 (1H, s)

## 10 EXAMPLE 96

2-(N'-n-Heptylureido)-5-dimethylamino-N-[1-(2-biphenylmethylpiperidin-4-yl)methyl]-benzamide

{2-amino-5-dimethylamino-N-[1-(2-biphenylmethylpiperidin-4-yl)methyl]benzamide and n-heptylamine } : mp 160 °C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)ppm : 0.84 (3H, t), 1.10-1.63 (15H, m), 1.78 (2H, t), 2.71 (2H, d), 2.84 (6H, s), 2.98 (2H, q), 3.11 (2H, t), 3.32 (2H, s), 6.80 (1H, d), 6.84 (1H, d), 6.91 (1H, bt), 7.21 (1H, dd), 7.28-7.44 (7H, m), 7.50 (1H, dd), 7.87 (1H, d), 8.52 (1H, bt), 9.22 (1H, s)

## EXAMPLE 97

20 2-(N'-n-Heptylureido)-5-dimethylamino-N-[[1-(dibenzosuberan-5-yl)piperidin-4-yl]methyl]benzamide

{2-amino-5-dimethylamino-N-[[1-(dibenzosuberan-5-yl)piperidin-4-yl]methyl]benzamide and n-heptylamine } : mp 207 °C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)ppm : 0.86 (3H, t), 0.98-1.96 (17H, m), 2.60 (2H, d), 2.74 (2H, q), 2.83 (6H, s), 2.96 (2H, q), 3.10 (2H, bt), 3.92 (4H, q), 3.98 (1H, s), 6.81 (2H, d), 6.89 (1H, bt), 6.98-7.29 (8H, m), 7.84 (1H, d), 8.51 (1H, bt), 9.13 (1H, s)

## EXAMPLE 98

2-(N'-n-Heptylureido)-5-dimethylamino-N-[(8-diphenylmethyl-8-azabicyclo[3.2.1]octan-3-yl)methyl]benzamide



{2-amino-5-dimethylamino-N-[(8-diphenylmethyl-8-azabicyclo[3.2.1]octan-3-yl)methyl] benzamide and n-heptylamine } : mp 195 °C; <sup>1</sup> H NMR (CDCl<sub>3</sub>)ppm : 0.88 (3H. t), 1.27 (8H. m), 1.49-1.61 (8H. m), 1.90-2.00 (1H. m), 1.99-2.02 (2H. m), 2.91 (6H. s), 3.17-3.22 (4H. m), 3.29-3.33 (2H. m), 4.44 (1H. s), 4.51 (1H. bt), 6.41 (1H. bt), 6.73 (1H. d), 6.85 (1H. dd), 7.13-7.28 (6H. m), 7.47 (4H. d), 7.96 (1H. d), 8.94(1H, s)

**EXAMPLE 99**

**2-(N'-n-Heptylureido)-5-dimethylamino-N-[1-methyl-1-(1-diphenylmethylpiperidin-4-yl)-ethyl]benzamide**

10 {2-amino-5-dimethylamino-N-[1-methyl-1-(1-diphenylmethylpiperidin-4-yl)ethyl]benzamide and n-heptylamine} : mp 190°C; <sup>1</sup> H NMR (CDCl<sub>3</sub>)ppm : 0.88 (3H. t), 1.27 (8H. m), 1.49-1.61 (8H. m), 1.90-2.00 (1H. m), 1.99-2.02 (2H. m), 2.91 (6H. s), 3.17-3.22 (4H. m), 3.29-3.33 (2H. m), 4.44 (1H. s), 4.51 (1H. bt), 6.41 (1H. bt), 6.73 (1H. d), 6.85 (1H. dd), 7.13-7.28 (6H. m), 7.47 (4H. d), 7.96 (1H. d), 8.94 (1H. s)

**EXAMPLE 100**

**5-Dimethylamino-2-(N'-n-pentylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide**

20 {2-amino-5-dimethylamino-N-[(diphenylmethylpiperidin-4-yl)methyl]benzamide and n-pentylamine} : mp 218°C; <sup>1</sup> H NMR (CDCl<sub>3</sub>)ppm : 0.88 (3H. t), 1.08-1.96 (13H. m), 2.75-3.00 (2H. m), 2.90 (6H. m), 3.18 (2H. q), 3.30 (2H. t), 4.25 (1H. s), 4.59 (1H. bt), 6.53 (1H. bt), 6.74 (1H. d), 6.82 (1H. dd), 7.05-7.52 (10H. m), 7.90 (1H. d), 8.92 (1H. s)

**EXAMPLE 101**

25 **2-(N'-Cyclobutylureido)-5-dimethylamino-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide**

{2-amino-5-dimethylamino-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide and cyclobutylamine} : mp 210-212°C; <sup>1</sup> H NMR (CDCl<sub>3</sub>)ppm : 1.30-1.90 (11H. m), 2.32 (2H. m), 2.89 (8H. s+m), 3.30 (2H. dd), 4.18 (1H. m),

4.26 (1H, s), 4.88 (1H, bs), 6.57 (1H, bs), 6.73 (1H, d), 6.81 (1H, d), 7.14-7.45 (10H, m), 7.89 (1H, d), 8.88 (1H, bs).

#### EXAMPLE 102

2-(N'-Cyclopentylureido)-5-dimethylamino-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide

{2-amino-5-dimethylamino-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide and cyclopentylamine} : mp 211-213°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 1.30-2.00 (15H, m), 2.90 (8H, s+m), 3.30 (2H, dd), 4.02 (1H, m), 4.24 (1H, s), 4.54 (1H, bs), 6.41 (1H, bs), 6.71 (1H, s), 6.83 (1H, d), 7.16-7.40 (10H, m), 7.97 (1H, d), 8.95 (1H, s).

#### EXAMPLE 103

2-(N'-3-Methoxypropylureido)-5-dimethylamino-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide

{2-amino-5-dimethylamino-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide and 3-methoxypropylamine} : mp 191-193°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 1.27-1.88 (9H, m), 2.92 (8H, m), 3.28 (7H, q+s), 3.41 (2H, t), 4.24 (1H, s), 4.88 (1H, bt), 6.60 (1H, bt), 6.77 (1H, d), 6.81 (1H, dd), 7.13-7.40 (10H, m), 8.00 (1H, d), 8.64 (1H, bs).

#### EXAMPLE 104

2-(N'-3-Methoxypropylureido)-5-(morpholin-4-yl)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide

{2-amino-5-(morpholin-4-yl)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide and 3-methoxypropylamine} : mp 175-176°C ; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 1.34-1.88 (9H, m), 2.90 (2H, m), 3.06 (4H, m), 3.31 (7H, m+s), 3.44(2H, t), 3.84 (4H, m), 4.24 (1H, s), 4.96 (1H, bt), 6.37 (1H, bt), 7.00 (1H, dd), 7.14-7.40 (10H, m), 8.10 (1H, d), 9.32 (1H, s).

#### EXAMPLE 105

2-(N'-Cyclopropylmethylureido)-5-(morpholin-4-yl)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide

{2-amino-5-(morpholin-4-yl)-N-[(1-diphenylmethylpiperidin-4-yl)-methyl]benzamide and cyclopropylmethylamine} : mp 218-220°C ; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.19 (2H, m), 0.48 (2H, m), 0.93 (1H, m), 1.34-1.88 (7H, m), 2.90 (2H, m), 3.06 (6H, m), 3.32 (2H, t), 3.84 (4H, m), 4.24 (1H, s), 4.69 (1H, bt), 6.34 (1H, bt), 6.89 (1H, d), 6.99 (1H, dd), 7.14-7.40 (10H, m), 8.15 (1H, d), 9.48 (1H, s).

The following compounds described in Examples 106 to 108 were prepared according to Example 26.

#### EXAMPLE 106

10 2-(N'-n-Heptylureido)-5-isopropyl-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide

{2-amino-5-isopropyl-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide and n-octanoic acid} : mp 179-180.5°C ; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.88 (3H, t), 1.22 (6H, d), 1.20-1.67 (13H, m), 1.69 (2H, d), 1.86 (2H, t), 2.84 (1H, m), 2.92 (2H, d), 3.23 (2H, dd), 3.32 (2H, t), 4.25 (1H, s), 4.53 (1H, t), 6.24 (1H, t), 7.14-7.42 (12H, m), 8.28 (1H, d), 10.03 (1H, s).

#### EXAMPLE 107

2-(N'-n-Heptylureido)-6-dimethylamino-N-(1-diphenylmethylpiperidin-4-yl)benzamide

20 {2-amino-6-dimethylamino-N-(1-diphenylmethylpiperidin-4-yl)benzamide and n-octanoic acid} : mp 77°C ; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.88 (3H, t), 1.10-1.30 (8H, m), 1.51 (2H, t), 1.61 (2H, m), 1.95 (2H, d), 2.13 (2H, t), 2.66 (6H, s), 2.76 (2H, d), 3.23 (2H, q), 3.97-4.05 (1H, m), 4.29 (1H, s), 4.52 (1H, bt), 6.74 (1H, d), 7.19 (1H, t), 7.26-7.43 (9H, m), 8.19 (1H, d), 9.82 (1H, bt), 11.10 (1H, s).

#### 25 EXAMPLE 108

2-(N'-n-Heptylureido)-4-dimethylamino-N-(1-diphenylmethylpiperidin-4-yl)benzamide

{2-amino-4-dimethylamino-N-(1-diphenylmethylpiperidin-4-yl)benzamide and n-octanoic acid} : mp 87°C ; <sup>1</sup>H NMR (CDCl<sub>3</sub>)ppm : 0.87 (3H, t), 1.18-1.70 (12H,

m), 1.96 (2H, d), 2.07 (2H, t), 2.83 (2H, d), 3.02 (6H, s), 3.24 (2H, q), 3.88-3.91 (1H, m), 4.27 (1H, s), 4.54 (1H, bt), 5.88 (1H, d), 6.23 (1H, dd), 7.10-7.51 (11H, m), 7.94 (1H, d), 11.01 (1H, s)

#### EXAMPLE 109

5 **5-Amino-2-(N'-n-butylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]-benzamide**

Step 1) : To a solution of 2-amino-5-nitro-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide (Preparation 28) (1.2g, 2.69mmol) in  $\text{CHCl}_3$  (15ml) was added n-butylisocyanate (802mg, 8.09mmol). After the solution was refluxed  
10 for 24 hours, the solvent was evaporated. The residue was purified by column chromatography on silica gel to give 5-nitro-2-(N'-n-butylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide, 1.1g (75%).

Step 2) : To a solution of 5-nitro-2-(N'-n-butylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide (960mg, 1.76mmol) in MeOH/AcOEt  
15 (50ml/50ml) was added  $\text{PtO}_2$  (38mg) and agitated under  $\text{H}_2$  atmosphere ( $3\text{kg/cm}^2$ ) until the reaction was complete. The catalysts were filtered off and the filtrate was evaporated. The residue was purified by column chromatography on silica gel to give 5-amino-2-(N'-n-butylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide, 780mg (86%); mp  $212-213^\circ\text{C}$ ;  $^1\text{H}$  NMR ( $\text{DMSO-d}_6$ ) ppm :  
20 0.83 (3H, t), 1.21-1.88 (11H, m), 2.77 (2H, m), 2.95 (2H, q), 3.10 (2H, t), 4.27 (1H, s), 4.80 (2H, bs), 6.58 (1H, dd), 6.68 (1H, d), 6.75 (1H, bt), 7.13-7.41 (10H, m), 7.58 (1H, d), 8.35 (1H, bt), 8.74 (1H, s).

In a similar manner to that of Example 109, but replacing n-butylisocyanate with n-propylisocyanate, the following compound (Example 110)  
25 was prepared.

#### EXAMPLE 110

**5-Amino-2-(N'-n-propylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]-benzamide**

{ n-propylisocyanate } : mp  $213-214^\circ\text{C}$ ;  $^1\text{H}$  NMR ( $\text{DMSO-d}_6$ ) ppm :

0.80 (3H, t), 1.21-1.82 (9H, m), 2.77 (2H, m), 2.92 (2H, q), 3.10 (2H, m), 4.27 (1H, s), 4.80 (2H, bs), 6.58 (1H, dd), 6.68 (1H, d), 6.78 (1H, bt), 7.14-7.41 (10H, m), 7.59 (1H, d), 8.34 (1H, bt), 8.75 (1H, s).

### EXAMPLE 111

5 (a) 2-(N'-n-Butylureido)-5-methylsulfinyl-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide

and (b) 2-(N'-n-butylureido)-5-methylsulfonyl-N-[(1-diphenylmethylpiperidin-4-yl)-methyl]benzamide

A solution of 5-methylthio-2-(N'-n-butylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl] benzamide( EXAMPLE 73 ) (200mg,0.367mmol) in CH<sub>3</sub>CN/CH<sub>2</sub>Cl<sub>2</sub>/MeOH/H<sub>2</sub>O (10ml/2ml/4ml /0.5ml) was agitated with OXONE<sup>®</sup> (2KHSO<sub>5</sub>,KHSO<sub>4</sub>K<sub>2</sub>SO<sub>4</sub>) (142mg, 0.231mmol) for 2 hours at room temperature and then anadditional OXONE<sup>®</sup> (15mg) was added. The reaction mixture was made basic with 25% NH<sub>4</sub>OH and diluted with CH<sub>2</sub>Cl<sub>2</sub> . The organic layer was washed twice with H<sub>2</sub>O, dried over MgSO<sub>4</sub> and evaporated. The residue was purified by column chromatography on silica gel to give 2-(N'-n-butylureido)-5-methylsulfinyl-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide. 130mg (63%) : mp 209-211°C ; <sup>1</sup> H NMR (CDCl<sub>3</sub>) ppm : 0.91 (3H, t), 1.33-1.88 (11H, m), 2.69 (3H, s), 2.88 (2H, m), 3.22-3.31 (4H, m), 4.24 (1H, s), 4.85 (1H, bt), 7.03 (1H, bt), 7.13-7.42 (11H, m), 7.91 (1H, d), 8.63 (1H, d), 10.71 (1H, s) ;  
20 and 2-(N'-n-butylureido)-5-methylsulfonyl-N-[(1-diphenylmethylpiperidin-4-yl)-methyl] benzamide. 30mg (14%) : mp 178-179°C ; <sup>1</sup> H NMR (CDCl<sub>3</sub>) ppm : 0.93(3H, t), 1.31-1.88 (11H, m), 2.90 (2H, m), 3.02 (3H, s), 3.23-3.34 (4H, m), 4.25 (1H, s), 4.79 (1H, bt), 6.61 (1H, bt), 7.13-7.40 (10H, m), 7.89 (1H, dd), 7.97 (1H, d), 8.73 (1H, d), 10.82 (1H, s), respectively.

### EXAMPLE 112

5-Methylamino-2-(N'-n-butylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide

Step 1) : A mixture of 2-amino-5-(N-tert-butoxycarbonyl-N-methyl)-

amino-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide (Preparation 25) (1.4g, 2.65mmol) and n-butyliisocyanate (1.4g, 14.12mmol) in  $\text{CHCl}_3$  (25ml) was refluxed for 8 hours and evaporated. The residue was purified by column chromatography on silica gel to give 5-(N-tert-butoxycarbonyl-N-methyl)amino-2-(N'-n-butylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide, 1.4g (84%).

Step 2) : A mixture of 5-(N-tert-butoxycarbonyl-N-methyl)amino-2-(N'-n-butylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide (1.4g, 2.23mmol) and trifluoroacetic acid (3 ml) was stirred under cooling in an ice-bath for 30 mins and at room temperature for 30 mins. The reaction mixture was poured into  $\text{H}_2\text{O}$ , made basic with  $\text{NaHCO}_3$  and extracted with  $\text{CHCl}_3$ . The extract was washed with  $\text{H}_2\text{O}$ , dried over  $\text{MgSO}_4$  and evaporated to give 5-methylamino-2-(N'-n-butylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide, 310mg (26.5%); mp 203-204°C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) ppm : 0.90 (3H, t), 1.28-1.87 (12H, m), 2.79 (3H, s), 2.89 (2H, d), 3.17 (2H, q), 3.27 (2H, t), 4.23 (1H, s), 4.62 (1H, t), 6.56-6.67 (3H, m), 7.13-7.40 (10H, m), 7.82 (1H, d), 8.86 (1H, s).

The following Examples (Example 113 and 114) illustrate pharmaceutical compositions according to the present invention and an "active ingredient" in these Examples is any compound of the formula(1) as hereinabove defined, preferably one of the compounds of Examples 1 to 112.

#### EXAMPLE 113

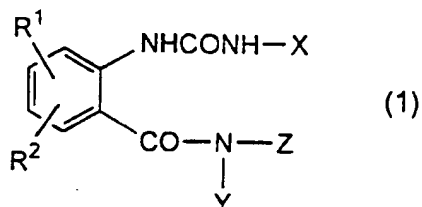
Tablet formulation : Tablets each containing 100mg of active ingredient, 200mg of lactose, 40mg of cellulose and 5mg of magnesium stearate were prepared in accordance with usual procedure.

#### EXAMPLE 114

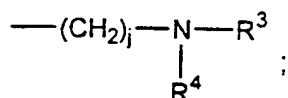
Capsule formulation : Hard-shell gelatin capsules each containing 50mg of active ingredient, 100mg of lactose, 30mg of cornstarch and 2mg of magnesium stearate were prepared in accordance with usual procedure.

CLAIMS

1. A 2-ureido-benzamide compound of the formula (1)

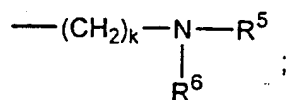


- in which  $\text{R}^1$  is H, halogen atom,  $(\text{C}_1\text{-C}_4)$ alkyl,  $(\text{C}_1\text{-C}_4)$ alkoxy or  $(\text{C}_1\text{-C}_4)$ dialkylamino and  $\text{R}^2$  is H, halogen atom, hydroxy, nitro,  $(\text{C}_1\text{-C}_4)$ alkyl,  $(\text{C}_1\text{-C}_4)$ alkoxy,  $(\text{C}_3\text{-C}_6)$  cycloalkylmethoxy,  $(\text{C}_1\text{-C}_4)$  alkylthio,  $(\text{C}_1\text{-C}_4)$  alkylsulfinyl,  $(\text{C}_1\text{-C}_4)$ alkylsulfonyl or

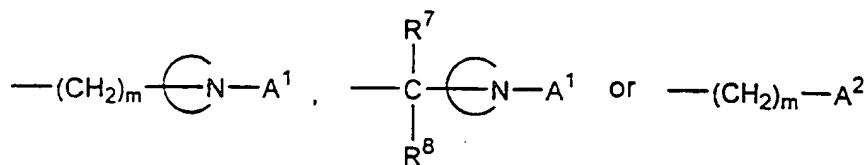


- wherein  $j$  is an integer of from 0 to 2 and  $\text{R}^3$  and  $\text{R}^4$  are each independently H,  $(\text{C}_1\text{-C}_4)$ alkyl,  $(\text{C}_1\text{-C}_4)$ alkanoyl,  $(\text{C}_1\text{-C}_4)$ alkylsulfonyl or  $(\text{C}_1\text{-C}_4)$ alkylcarbamoyl,  $\text{NR}^3\text{R}^4$  can form a pyrrolidine, piperidine, morpholine, imidazole or pyrazole ring;

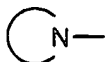
X is a  $(\text{C}_3\text{-C}_{15})$ alkyl,  $(\text{C}_3\text{-C}_6)$  cycloalkyl,  $(\text{C}_3\text{-C}_6)$  cycloalkylmethyl,  $\omega\text{-(C}_1\text{-C}_4)$  alkoxy- $(\text{C}_1\text{-C}_4)$  alkyl group or



- wherein  $k$  is an integer of from 1 to 4 and  $\text{R}^5$  and  $\text{R}^6$  are each independently H,  $(\text{C}_1\text{-C}_6)$  alkyl or  $(\text{C}_1\text{-C}_4)$ alkoxycarbonyl; and  
Y is H or  $(\text{C}_1\text{-C}_4)$ alkyl and Z is

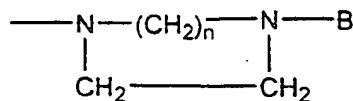


wherein m is an integer of from 0 to 4.



is a pyrrolidiny or piperidyl ring and  $A^1$  is a phenyl, benzyl, diphenylmethyl, pyridyl, dibenzoxepiny, phenoxy carbonyl or biphenylmethyl group optionally carrying halogen atom, hydroxy,  $(C_1-C_7)$ alkyl,  $(C_1-C_4)$ alkoxy,  $(C_1-C_4)$ alkoxymethyl, phenyl or halogenophenyl, and  $A^2$  is a phenyl, benzyl, diphenylmethyl, dibenzoxepiny or phenoxy carbonyl group optionally carrying halogen atom, hydroxy,  $(C_1-C_7)$ alkyl,  $(C_1-C_4)$ alkoxy,  $(C_1-C_4)$ alkoxymethyl, phenyl or halogenophenyl, and  $R^7$  is H or  $(C_1-C_4)$ alkyl and  $R^8$  is  $(C_1-C_4)$ alkyl or  $NR^7R^8$  can form a cyclopentyl, cyclohexyl or cycloheptyl ring; or

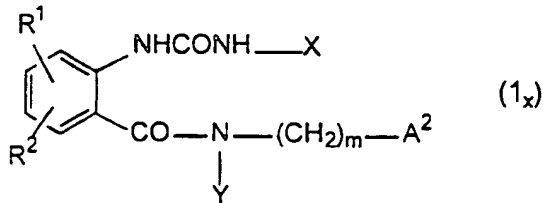
-NYR can form a ring



wherein n is an integer of from 1 to 3 and B is a phenyl, diphenylmethyl or dibenzocycloheptenyl group optionally carrying halogen atom or  $(C_1-C_4)$ alkoxy;

and pharmaceutically acceptable acid addition salts thereof.

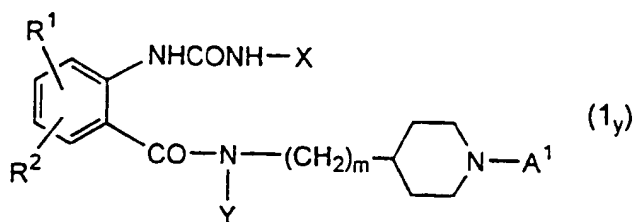
2. A compound of claim 1 in which the 2-ureido-benzamide derivative of the formula (1) is a compound of the formula (1x)



wherein  $R^1$  is H; X is  $(C_3-C_{10})$ alkyl; and Y is H.

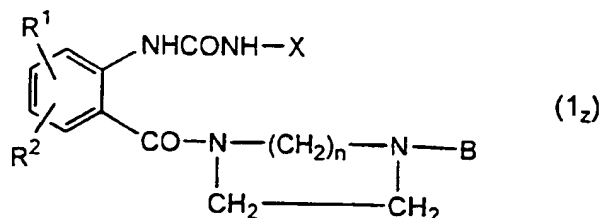


3. A compound of claim 1 in which the 2-ureido-benzamide derivative of the formula (1) is a compound of the formula (1y)



wherein R<sup>1</sup> is H; X is (C<sub>3</sub>-C<sub>10</sub>)alkyl; and Y is H.

- 5 4. A compound of claim 1 in which the 2-ureido-benzamide derivative of the formula (1) is a compound of the formula (1z)



wherein R<sup>1</sup> is H and X is (C<sub>3</sub>-C<sub>10</sub>)alkyl.

5. A compound of claim 2 of the formula (1x) wherein R<sup>2</sup> is H; X is (C<sub>3</sub>-C<sub>8</sub>)alkyl; m is 1 or 2; and A<sup>2</sup> is diphenylmethyl or dibenzoxepinyl.
- 10 6. A compound of claim 3 of the formula (1y) wherein R<sup>2</sup> is H, di(C<sub>1</sub>-C<sub>4</sub>)alkylamino or morpholinyl; X is (C<sub>3</sub>-C<sub>8</sub>) alkyl; m is 0, 1 or 2; and A<sup>1</sup> is diphenylmethyl optionally carrying halogen atom or (C<sub>1</sub>-C<sub>4</sub>) alkoxy on the phenyl ring or phenoxy carbonyl.
- 15 7. A compound of claim 4 of the formula (1z) wherein R<sup>2</sup> is H; n is 2 or 3; and B is diphenylmethyl or dibenzocycloheptenyl.
8. A compound of any one of claims 1 to 7 in which the 2-ureido-benzamide derivative of the formula (1) is
- 2-(N'-n-heptylureido)-5-dimethylamino-N-[(1-diphenylmethylpiperidin-4-yl)-methyl]-benzamide;
- 20 2-(N'-n-butylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide;
- 2-(N'-n-pentylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide;

- 2-(N'-n-hexylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide;  
2-(N'-n-heptylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide;  
2-(N'-n-octylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide;  
2-(N'-n-butylureido)-N-(1-diphenylmethylpiperidin-4-yl)benzamide;  
5 2-(N'-n-hexylureido)-N-(1-diphenylmethylpiperidin-4-yl)benzamide;  
2-(N'-n-octylureido)-N-(1-diphenylmethylpiperidin-4-yl)benzamide;  
2-(N'-n-decylureido)-N-(1-diphenylmethylpiperidin-4-yl)benzamide;  
2-(N'-n-heptylureido)-N-(1-phenoxy-carbonylpiperidin-4-yl)benzamide;  
2-(N'-n-heptylureido)-5-hydroxy-N-(3,3-diphenylpropyl)benzamide;  
10 2-(N'-n-heptylureido)-N-[2-(1-diphenylmethylpiperidin-4-yl)ethyl]benzamide;  
2-(N'-n-pentylureido)-N-[2-(1-diphenylmethylpiperidin-4-yl)ethyl]benzamide;  
2-(N'-n-hexylureido)-N-[2-(1-diphenylmethylpiperidin-4-yl)ethyl]benzamide;  
2-(N'-n-heptylureido)-5-dimethylamino-N-(1-diphenylmethylpiperidin-4-yl)-  
benzamide;  
15 1-[2-(N'-n-heptylureido)benzoyl]-4-diphenylmethylhomopiperazine;  
1-[2-(N'-n-heptylureido)benzoyl]-4-(10,11-dihydro-5H-dibenzo[a,b]cyclohepten-  
5-yl)-piperazine;  
2-(N'-n-heptylureido)-N-(1-diphenylmethylpiperidin-4-yl)benzamide;  
N-(2-bromo-6,11-dihydrodibenz[b,e]oxepin-11-yl)methyl-2-(N'-n-heptylureido)-  
20 benzamide;  
2-(N'-n-heptylureido)-5-acetoamido-N-(1-diphenylmethylpiperidin-4-yl)benza-  
mide;  
N-(3,3-diphenylpropyl)-2-(N'-n-heptylureido)benzamide;  
1-[2-(N'-n-heptylureido)benzoyl]-4-diphenylmethylpiperazine;  
25 2-(N'-n-butylureido)-5-diethylamino-N-[(1-diphenylmethylpiperidin-4-yl)me-  
thyl]benzamide;  
2-(N'-n-butylureido)-5-dimethylamino-N-[(1-diphenylmethylpiperidin-4-yl)me-  
thyl]benzamide;  
2-(N'-n-butylureido)-5-(pyrrolidin-1-yl)-N-[(1-diphenylmethylpiperidin-4-yl)-

- methyl]benzamide;
- 5-dimethylamino-2-(N'-n-propylureido)-N-[(1-diphenylmethylpiperidin-4-yl)-methyl]benzamide;
- 2-(N'-butylureido)-5-methoxy-N-[(1-diphenylmethylpiperidin-4-yl)methyl]-
- 5 benzamide;
- 2-(N'-n-butylureido)-5-ethoxy-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide;
- 2-(N'-n-butylureido)-5-cyclopropylmethoxy-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide;
- 10 2-(N'-n-butylureido)-5-(morpholin-4-yl)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide;
- 5-(morpholin-4-yl)-2-(N'-n-propylureido)-N-[(1-diphenylmethylpiperidin-4-yl)-methyl]benzamide;
- 2-(N'-n-butylureido)-5-methylthio-N-[(1-diphenylmethylpiperidin-4-yl)methyl]-
- 15 benzamide;
- 5-n-butylcarbamyloxy-2-(N'-n-butylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]-benzamide;
- 2-(N'-n-heptylureido)-5-methoxy-N-[(1-diphenylmethylpiperidin-4-yl)methyl]-benzamide;
- 20 2-(N'-n-heptylureido)-5-(morpholin-4-yl)-N-[(1-diphenylmethylpiperidin-4-yl)-methyl]benzamide;
- 2-(N'-n-heptylureido)-5-(pyrazol-1-yl)-N-[(1-diphenylmethylpiperidin-4-yl)-methyl]benzamide;
- 2-(N'-n-heptylureido)-5-(pyrrolidin-1-yl)-N-[(1-diphenylmethylpiperidin-4-yl)-
- 25 methyl]benzamide;
- 5-ethoxy-2-(N'-n-heptylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]-benzamide;
- 2-(N'-n-heptylureido)-5-dimethylamino-N-[(1-diphenylmethylpiperidin-3-yl)-methyl]benzamide;

5-(N-acetyl-N-methyl)amino-2-(N'-n-heptylureido)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide;

2-(N'-n-heptylureido)-5-dimethylamino-N-[[1-bis(4-fluorophenyl)methylpiperidin-4-yl)methyl]benzamide;

5 2-(N'-n-heptylureido)-5-dimethylamino-N-[[1-bis(4-methoxyphenyl)methylpiperidin-4-yl)-methyl]benzamide;

2-(N'-n-heptylureido)-5-dimethylamino-N-[1-(2-biphenylmethylpiperidin-4-yl)-methyl]benzamide;

5-dimethylamino-2-(N'-n-pentylureido)-N-[(1-diphenylmethylpiperidin-4-yl)-methyl]benzamide;

2-(N'-3-methoxypropylureido)-5-dimethylamino-N-[(1-diphenylmethylpiperidin-4-yl)-methyl]benzamide

2-(N'-3-methoxypropylureido)-5-(morpholin-4-yl)-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide;

15 2-(N'-cyclopropylmethylureido)-5-(morpholin-4-yl)-N-[(1-diphenylmethylpiperidin-4-yl)-methyl]benzamide;

2-(N'-n-butylureido)-5-methylsulfinyl-N-[(1-diphenylmethylpiperidin-4-yl)methyl]benzamide;

20 2-(N'-n-butylureido)-5-methylsulfonyl-N-[(1-diphenylmethylpiperidin-4-yl)methyl]-benzamide.

9. A pharmaceutical composition for inhibiting acyl-CoA:cholesterol acyltransferase which comprises a 2-ureido-benzamide derivative of any one of claims 1 to 8 and a pharmaceutically acceptable carrier, excipient or diluent.

10. A pharmaceutical composition for inhibiting macrophagic acyl-CoA:cholesterol acyltransferase which comprises a 2-ureido-benzamide derivative of any one of claims 1 to 8 and a pharmaceutically acceptable carrier, excipient or diluent.

11. A pharmaceutical composition for inhibiting accumulation of cholesterol ester in arterial wall which comprises a 2-ureido-benzamide derivative of any one

of claims 1 to 8 and a pharmaceutically acceptable carrier, excipient or diluent.

12. The use of a 2-ureido-benzamide derivative of any one of claims 1 to 8 for the production of a medicine for use in the prevention and treatment of disorders or diseases associated with acyl-CoA:cholesterol acyltransferase, such as
- 5 atherosclerosis.

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 96/01836

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D211/26 C07D211/56 C07D211/58 C07D213/75 C07D207/09  
C07D233/54 C07D233/84 C07D295/18 C07D313/12 C07D401/06  
C07D401/12 C07D405/04 C07C275/28 C07C275/34 C07C313/16

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JOURNAL OF MEDICINAL CHEMISTRY, vol. 36, no. 11, 1993, pages 1641-1653, XP000196262 T. KIMURA ET AL.: "Structure-Activity Relationship of a Series of Phenylureas Linked to 4-Phenylimidazole. Novel Potent Inhibitors of Acyl-CoA:Cholesterol O-Acyltransferase with Antiatherosclerotic Activity. 2" cited in the application see page 1641, abstract and left-hand column, first paragraph; page 1646, compound 38; Table III ---	1,2,9-12
Y	EP,A,0 477 778 (EISAI CO., LTD.) 1 April 1992 cited in the application see claims 1,18-23; example 158 ---	1,2,9-12
-/--		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- \*&\* document member of the same patent family

Date of the actual completion of the international search

22 August 1996

Date of mailing of the international search report

06.09.96

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Hass, C

# INTERNATIONAL SEARCH REPORT

Int. Application No

PCT/EP96/01836

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07C317/14 C07C321/28 A61K31/17 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,4 623 662 (V.G. DE VRIES) 18 November 1986 cited in the application see column 9, line 17 - line 39; claim 1 ---	1,9-12
A	EP,A,0 335 374 (WARNER-LAMBERT CO.) 4 October 1989 see claims 1,3,4 & US,A,5 116 848 cited in the application ---	1,9-12
A	EP,A,0 335 375 (WARNER-LAMBERT CO.) 4 October 1989 cited in the application see claims 1,4,5 ---	1,9-12
-/--		

☒ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

### \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- \*&\* document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentaan 2  
NL - 2280 HV Rijswijk  
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,  
Fax (+ 31-70) 340-3016

Authorized officer

## INTERNATIONAL SEARCH REPORT

Inte. national Application No

PCT/EP96/01836

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PATENT ABSTRACTS OF JAPAN vol. 9, no. 36 (C-266), 15 February 1985 & JP,A,59 181257 (CHUGAI SEIYAKU K.K.), 15 October 1984, see abstract; example; formula I ---	1
A	EP,A,0 235 878 (BEECHAM GROUP PLC) 9 September 1987 cited in the application see page 27, compound 34 ---	1
A	INDIAN JOURNAL OF CHEMISTRY, vol. 26b, no. 12, 1987, pages 1133-1139, XP000196273 B.P. ACHARYA ET AL.: "Structure of the 2-Isocyanatobenzoyl Chloride-Aluminium Chloride (1:2) Complex: Reactions with Some Nucleophiles" cited in the application see page 1134, compound 16 ---	1
A	MONATSHFTE FÜR CHEMIE, vol. 98, no. 3, 1967, pages 633-642, XP000578294 W. METLESICS ET AL.: "Chinazoline und 1,4-Benzodiazepine, 35. Mitt." cited in the application see page 638, compound 15 ---	1
A	US,A,3 812 168 (K. HOEGERLE ET AL.) 21 May 1974 cited in the application see column 1, abstract ---	1
A	EP,A,0 105 196 (HOECHST AG) 11 April 1984 see claim 1 -----	1



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 96/01836

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-477778	01-04-92	AT-T- 137220	15-05-96
		AU-B- 648338	21-04-94
		AU-B- 8469291	02-04-92
		CA-A- 2052191	26-03-92
		CN-A- 1060466	22-04-92
		DE-D- 69119013	30-05-96
		EP-A- 0615970	21-09-94
		ES-T- 2087936	01-08-96
		JP-A- 5092950	16-04-93
KR-B- 9403494	23-04-94		
-----			
US-A-4623662	18-11-86	US-A- 5003106	26-03-91
-----			
EP-A-335374	04-10-89	US-A- 5116848	26-05-92
		DE-T- 68907359	04-11-93
		ES-T- 2056992	16-10-94
		JP-A- 2006455	10-01-90
		JP-B- 7025728	22-03-95
-----			
EP-A-335375	04-10-89	US-A- 4868210	19-09-89
		DE-T- 68906940	28-10-93
		ES-T- 2055754	01-09-94
		HK-A- 148295	22-09-95
		JP-A- 2006457	10-01-90
		JP-B- 6088957	09-11-94
		US-A- 4948806	14-08-90
		US-A- 4999373	12-03-91
		US-A- 5030653	09-07-91
-----			
EP-A-235878	09-09-87	AU-B- 603350	15-11-90
		AU-B- 6756787	23-07-87
		JP-A- 62209077	14-09-87
		US-A- 4797387	10-01-89
-----			
US-A-3812168	21-05-74	CH-A- 504414	15-03-71
		DE-A- 1916051	16-10-69
		FR-A- 2005140	05-12-69
		GB-A- 1265676	01-03-72
		US-A- 3646136	29-02-72
		US-A- 3806334	23-04-74

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 96/01836

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-105196	11-04-84	DE-A- 3232959	08-03-84
		AU-B- 1867983	08-03-84
		CA-A- 1214182	18-11-86
		JP-A- 59076050	28-04-84
		US-A- 4504490	12-03-85
-----			